The Journal of Pediatrics

VOL. 7 AUGUST, 1935 NO. 2

Original Communications

NEUROBLASTOMA OF THE ADRENAL IN CHILDREN

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INTRODUCTION

THE medulla of the adrenal, although composed of specialized chromaffin tissue, has its origin in more primitive neural elements common to the entire sympathetic nervous system.

The most frequent malignant tumor occurring in this organ arises during the development of this chromaffin tissue and shows a microscopic composition of undifferentiated cells referred to as neuroblasts or sympathoblasts. These neuroblastomas or sympathoblastomas of the adrenal medulla are usually seen in patients under the age of three years, are rapidly fatal, and metastasize to the liver, lymph nodes, bones, eyes, lungs and other organs. Over 160 cases have been reported in the literature to date.

The undifferentiated masses of sympathetic tissue destined to form the adrenal medulla migrate outward from the primitive neural tube in the first few weeks of embryonic life along with other groups of primitive building cells which form the paraganglia of the sympathetic system. Malignant sympathetic tumors, therefore, in the region of the adrenal medulla, do not differ in pathologic structure from the primitive sympathetic tumors occurring in the vertebral ganglia in the cervical, thoracic, and abdominal regions or other primitive neurogenic tumors common in children, namely, the retinoblastomas of the eye and the medulloblastomas of the cerebellum.

Historical Note.—Although Virchow[1] (1864) is credited as the first to recognize the nature of these malignant adrenal tumors in children, he referred to them as gliomas. Marchand[2] (1891) was probably the first to recognize the true neural structure of these neoplasms, but in spite of his observations the early reports up to

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1910 refer to these growths most frequently as round cell sarcomas, lymphosarcomas, or gliomas. The contribution of Wright[3] (1910) established their true pathologic nature, and the papers of Pepper[4] (1901) and Hutchinson[5] (1907) described the characteristic clinical pictures of the disease.

Dunn[6] in 1915 and Lehman[7] in 1917 carefully reviewed the literature and analyzed the case reports up to that time. Lehman's review thoroughly established the relationship between the histogenesis of these tumors and the development of the sympathetic system. He also reported the first case to be cured by surgery. The article by Scott, Oliver, and Oliver[8] (1933) reviews the literature to date, bringing the total number of cases to 162.

Basis of Present Study.—The present study is based upon seventeen cases of neuroblastoma of the adrenal occurring in children. Twelve of these cases have been studied clinically in the Harriet Lane Home of the Johns Hopkins Hospital. In six cases biopsy was performed, and in the remaining six cases autopsy was obtained. In the other five cases pathologic material was obtained at autopsy performed elsewhere, or tissue from biopsy was referred to the Surgical Pathological Laboratory of the Johns Hopkins Hospital for diagnosis. In each, the clinical records of the case were made available to us. In eleven of the seventeen cases an autopsy was performed. This series of cases afforded an excellent opportunity to review the salient clinical and pathologic features of these neoplasms and the problem of their differential diagnosis.

CLINICAL FEATURES

Etiologic Factors.—In the present series of cases the ages were practically equally distributed below and above two years; in eight instances the ages were two years or under and in nine over two years. Males predominated over females in the ratio of 11:5. In the one instance in which the sex was not mentioned, autopsy was performed elsewhere. This was the case of a stillborn infant in which metastases from an adrenal tumor to the liver caused obstruction to labor. Morcellation was necessary in making delivery of the fetus. The eldest child was aged thirteen years. The location of the tumors was equally distributed between the right and left adrenal (Table I). In two of the cases originating in the left adrenal, the right adrenal was involved, apparently by metastases.

Trauma was recorded in five of our cases, occurring from three months to one year prior to the onset of symptoms. No etiologic connection with the development of the tumor, however, could be established.

Pepper's conception of these growths as congenital in origin is supported by their microscopic structure, which shows a series of early neuroblastic forms which parallel in character and sequence the normal histogenesis of the adrenal medulla. It is not at all improbable that the impetus to proliferation inherent in this type of tissue in late

embryonic life is carried over in those cases in which the tumor occurs in the first few weeks of life. This relationship to normal development is discussed in the chapter on histogenesis.

TABLE I

ETIOLOGIC FACTORS IN 17 CASES OF NEUROBLASTOMA

Age			
	Birth to 6 mo.	3	
	6 mo. to 1 yr.	1	
	1 to 2 yr.	4	
	2 to 3 yr.	2	
	3 to 4 yr.	2	
	4 to 5 yr.	1	
	5 to 6 yr.	2	
	6 to 7 yr.	0	
	7 to 8 yr.	0	
	8 to 9 yr.	1	
	Over 9 yr.	1	
Sex			
	Males	11	
	Females	5	
	Not given	1	
Trauma			
	Abdominal trauma	5	(Occurring from 3 months to one year before onset of symptoms)
Side affected			
	Right	7	
	Left	7	
	Bilateral	2	
	Not stated	1	

Symptoms.—The commonest complaint on admission in our series of cases was the presence of an abdominal mass which was usually neither tender nor painful. This finding was noted in fifteen cases. The parent's attention had been attracted to the mass either because of attacks of vomiting or because the enlargement had become prominent enough to be noted in dressing or bathing. Vomiting was noted in nine cases, but it was not extreme or persistent. In nine cases fever was noted before the patient was brought to the clinic. Abdominal pain was a prominent symptom in six cases and was associated with vomiting in most instances. In three cases in which there was a combination of abdominal pain, vomiting and fever, a clinical diagnosis of appendiceal abscess was made. In six cases loss of weight was cited as the chief reason for bringing the patient to the physician. Emaciation, however, was not extreme in any of the early cases. Exophthalmos, when noted, was always a late sign. Joint pain was a relatively rare finding in the series. It was mentioned but not prominent in two cases, but in a third case this was the outstanding symptom. Pain in the region of the hips had been present for months, and

a diagnosis of osteomyelitis or tuberculosis was considered as a likely diagnosis even after the patient's admission and study in the clinic. In the other two instances the joint pain led to the diagnosis of rheumatic fever. Frew[9] called attention to such a case. A list of the major symptoms is given in Table II. Abdominal mass, fever, and pallor are also listed under the major physical findings shown in Table III. Although feverishness was noted by the parents in only nine cases, some elevation of temperature was found in all cases observed in the hospital over a sufficient period. Although the cause of this fever has not been ascertained, it is a common finding in all rapidly growing and malignant neoplasms occurring in the young.

TABLE II

SYMPTOMS IN 17 CASES OF NEUROBLASTOMA

Abdominal mass	15	Pain in joints or bones	3
Fever	9	Restlessness	2
Vomiting	9	Constipation	2
Abdominal pain	6	Diarrhea	1
Loss of weight	6	Poor cry from birth*	1
Anorexia	5	Crying at night	1
Pallor	4	Diminished activity	1
Exophthalmos, discoloration of lid	4	Dyspnea	1
General glandular enlargement	4	Precordial distress	1

*This was a three-week-old child who cried very little from birth, and who was found to have a large abdomen while being bathed.

TABLE III

FINDINGS IN 17 CASES OF NEUROBLASTOMA

Abdominal mass	15
Fever (100-102° F., 8 cases; 102-106° F., 6 cases)	14
Pallor	9
Enlarged liver (with enlarged spleen, 1 case)	8
Leucocytosis (14,000-23,000; normal differential)	7
Bone involvement in roentgenogram	6
Undernutrition	5
Metastatic nodules (thyroid, 3; skull, 1; parotid, 1)	5
Enlargement of lymph nodes	4
Eye signs, Exophthalmos (Swelling in orbit, diminished vision, dissolution of eyelid)	4
Anemia (under 3,000,000)	4
Tenderness (abdominal, 1; bones, 1; joints, 1)	3
Dilated veins (abdomen, 1; forehead, 1)	2
Ascites	2
Petechiae	1
Positive urinary findings (hematuria and albuminuria)	1

Findings.—Since the contributions of Hutchinson and of Pepper, both prior to 1910, the clinical features of neuroblastoma have been divided into two types based upon the seat of the metastases. In the first type, described by Pepper, the outstanding features are the abdominal enlargement (produced by metastatic involvement of the liver) and the appearance of the disease shortly after birth. In the

Hutchinson's syndrome, observed usually after the second year, the striking changes are in the bones of the skull, especially about the orbits, and in the blood.

Pepper's original contribution emphasized the early age at which the tumor appears (from three to eleven weeks old), the rapidly fatal course, and the enlargement of the liver without ascites or jaundice. Pepper made a point of the involvement of the right adrenal. In Pepper's original six cases three had involvement of the right adrenal; one, of the left adrenal; one was bilateral. In the sixth case the condition of the adrenal was not recorded. All of Pepper's cases occurred in females. The involvement of the liver in the Pepper syndrome was attributed by some subsequent observers to the origin of the tumor in the right adrenal. These earlier attempts to explain the distinction between the Pepper syndrome with hepatic metastases and the Hutchinson syndrome with osseous metastases on the basis of the location of the primary growth in the right or left adrenal have since proved untenable. The recent statistics compiled by Scott, Oliver, and Oliver show that the primary tumor may be situated either on the right or left side in both syndromes and that the most significant difference is one of age (average 12.7 months for the Pepper type compared with 6.9 years for the Hutchinson's syndrome). The earlier age of the patients showing the Pepper type of neuroblastoma of the adrenal may account for the more rapid and invasive course in this group of cases. Since the adrenals are in immediate contact with the liver, these more malignant growths tend to invade this organ by direct extension or via the anastomosing superficial vessels.

Hutchinson described "a definite clinical syndrome" in ten cases of suprarenal sarcoma with metastasis in the skull. All cases were in children. His original description is quoted in part: "In the majority of the cases the first thing noticed was some swelling about the bones of the skull, which in several of them was ascribed to a fall or injury. Following or sometimes preceding this, proptosis of one or both eyes was observed. In two-thirds of the cases discoloration of the eyelids on one or both sides is reported, and in a few instances this was the first point to attract attention. Anemia is a striking feature in all the cases, the blood changes being those of a profound secondary anemia. Leucocytosis has not been recorded in any case. An abdominal tumor in one or the other loin was felt in only five of the cases. The progress of the disease in every instance has been rapid, and the younger the patient the more rapid it appears . . ." The advance of the growth is marked by "indications of increased intracranial pressure such as torpor, intense optic neuritis, and blindness . . . the postmortem features are also very constant, in all there was found a sarcoma of the suprarenal, usually consisting of small round cells, situated on the left

side in six and on the right side in four of the cases. The most extensive metastases were found in the bones of the vault and base of the skull, producing the swellings on the head and protrusion of the eyes observed during life. . . . Metastases are also met with in the ribs, sternum, and vertebrae, but not, apparently (except in Case 1) in the long bones, though these may not always have been carefully examined."

Observations in our own cases show an overlapping of the Pepper and Hutchinson's syndromes (Fig. 3). In cases in which the bones are involved, there may also be abdominal enlargement due to metastases to the liver, and enlargement of the regional lymph nodes may occur in either type. While anemia is a more pronounced feature with the Hutchinson's syndrome, severe secondary anemia may also occur in the advanced stages of the Pepper type.

Fig. 1.—(H. L. H. 42879. Case 6.) Roentgenogram of a case of neuroblastoma of the Hutchinson type showing characteristic involvement of the long bones. There is an area of wedge-shaped bone resorption behind the epiphyseal line in the lower radius. Overlying this there is a faint periosteal reaction. The patient was a male infant aged sixteen months, with enlargement of the regional lymph nodes, fever, and a palpable mass in the left side.

Although the absence of ascites was considered one of the prominent clinical features of his cases by Pepper, ascites was present in two instances in our series when the abdominal cavity was opened at autopsy.

It is important from the standpoint of diagnosis to observe that the retroperitoneal mass in the region of the kidney may be very large without producing renal symptoms and that hepatic enlargement may progress to a marked degree without jaundice or ascites. There are exceptions to this rule. In one child of fifteen months (Case 1) with a neuroblastoma of the left adrenal and with large retroperitoneal nodes involved by metastases, the pyelogram showed a shifting of the left renal pelvis downward and inward. In another case of a colored boy nine years old (Case 4), the tumor originated in the right adrenal, metastasized to the left adrenal, and secondary deposits were found in both kidneys and nearly all the internal viscera. This patient showed red blood cells in the urine and nonprotein nitrogen retention.

A colored male, aged two (Case 5), with metastases involving both the liver and kidney showed ascites at autopsy. Ascites was also found at autopsy in Case 15. The patient was a white male aged four years. At autopsy the peritoneum was studded with metastases. Metastases were also found in the liver and in the right kidney. The primary mass was at the site of the left adrenal and measured 15×17 cm.

ROENTGENOGRAPHIC FEATURES

In this present group x-ray studies were made in nine patients. Case 1 and Case 4 showed no changes in any of the bones although both had a large shadow in the abdomen. These were both instances of

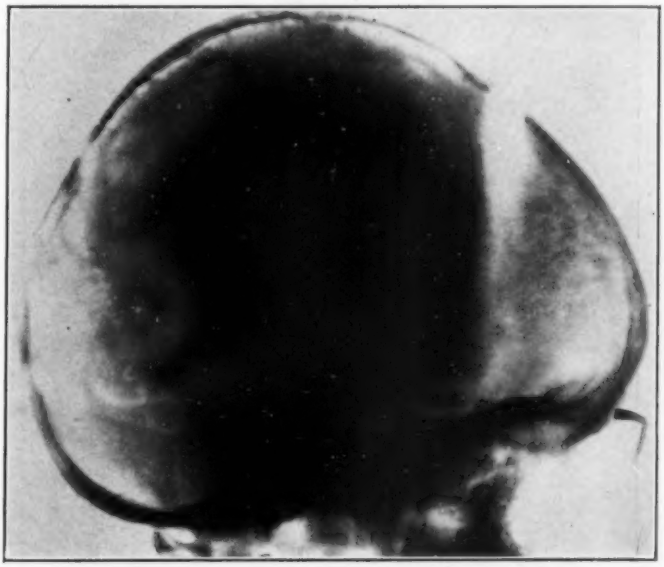

Fig. 2.—H. L. H. 79043. Case 11.) Involvement of the skull in a white male, aged three years, with a typical Hutchinson's syndrome. There was bilateral exophthalmos with discoloration of the eyelids. The roentgenogram of the skull shows separation of the sutures and numerous minute defects in the frontal and parietal bones. There were similar areas of resorption in the long bones.

typical Pepper syndromes. In Cases 2, 9, and 10, x-ray examinations of the abdomen and skeleton were negative.

In Case 6 bone involvement was depicted in the roentgenogram. Both humeri showed areas of resorption in the upper portion just distal to the epiphyseal line. Similar areas of resorption were present in the lower ends of the radius, the upper end of the left tibia and fibula, and upper right fibula. The zones of destruction were wedge-shaped, extending from the region of the cortex into cancellous bone. There was no overlying periosteal reaction (Fig. 1).

Case 11 showed extensive changes in the skull, long bones, and ribs. The sutures of the skull were separated and numerous minute defects were present in the frontal and parietal bones (Fig. 2). Similar foci of resorption were present in the humeri, radii, ulnae, clavicles, and ribs. These changes occurred in both the ends and in the midshaft region of the long bones.

In Case 3, since repeated x-ray studies were made over a period of two months, the progressive changes in the bones could be followed. At the first x-ray examination (Mar. 26, 1934) the bones were nega-

Fig. 3.—(H. L. H. 55657. Case 3.) Roetgenogram of the pelvis showing bone involvement above the lesser trochanter of the left femur. The film was taken Mar. 26, 1934 (right and left have been reversed in reproduction). All other bones were negative at that time. The patient was a white female aged five years, who had been admitted because of joint symptoms and fever. Figs. 3 to 8 inclusive show progressive skeletal involvement in this case.

tive except for the left femur (Fig. 3). Bone destruction was present just below the trochanteric region, the adjoining bone substance showing increased density. The adjacent periosteum was raised slightly. About two weeks later (Apr. 12, 1934) (Fig. 4) the x-ray findings were similar except that the periosteal reaction overlying the area in the left femur was slightly more pronounced. Six weeks later (May 25, 1934), approximately two months after the first examination, practically the entire skeleton was involved. Both the upper right and

Fig. 4.—(H. L. H. 55657. Case 3.) Roentgenogram of the pelvis made Apr. 12, 1934. A slight overlying periosteal reaction is the only noticeable change (compare with Fig. 3).

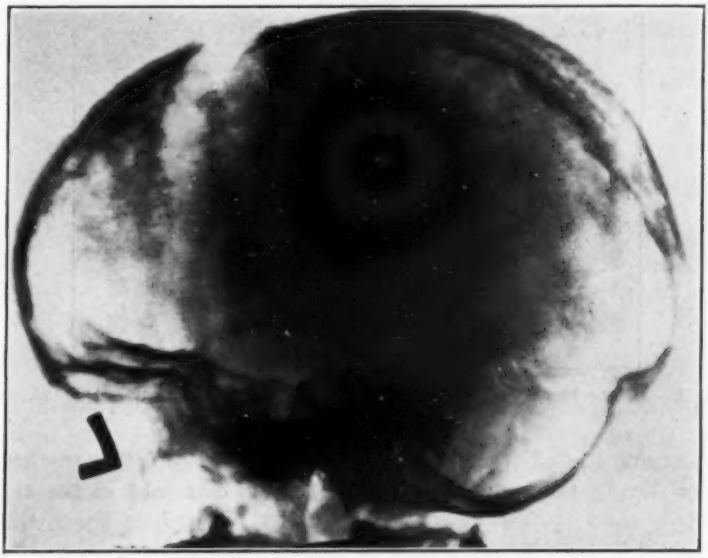

Fig. 5.—(H. L. H. 55657. Case 3.) Roentgenogram of the skull May 25, 1934. The entire skeleton is involved by multiple areas of bone resorption with some increase in bone density in neighboring areas (see Figs. 6, 7, and 8).

upper left femur showed a moth-eaten appearance. Occasional foci of resorption, slightly larger and more distinct than the others, could be noted, but in general there was a diffuse osteoporosis (with mottling produced by some increased density) in all the long bones of the lower extremities and in the skull and pelvis. In the upper left humerus there was a sharply demarcated area of bone resorption involving the

Fig. 6.—(H. L. H. 55657. Case 3.) Roentgenogram of the pelvis, May 25, 1934 (compare with Figs. 3 and 4).

cortex and the adjacent cancellous substance. The defect was characteristically wedge-shaped. These studies show that in the x-ray films in cases of neuroblastoma involvement of the long bones, spine, or pelvis may precede involvement of the skull in patients who eventually develop a Hutchinson's syndrome. The metaphyseal regions of the long bones show the earliest and most pronounced areas of resorp-

tion, which are characteristically wedge-shaped in appearance. A periosteal reaction may overlie the defect. The skull was involved in the region of the calvarium. Here the metastases gave minute foci of destruction resulting in a worm-eaten appearance (Figs. 5 to 8).

In cases of the Pepper syndrome x-rays of the abdomen may show a diffuse mass clouding on the affected side overlapping the shadow

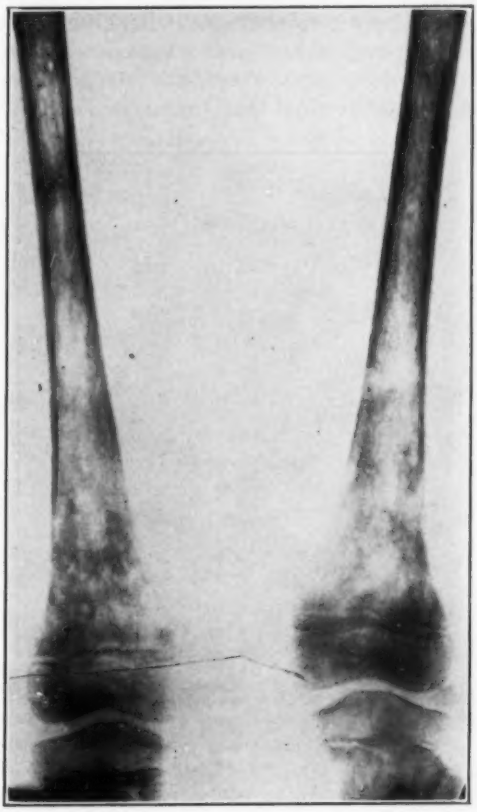

Fig. 7.—(H. L. H. 55657. Case 3.) Roentgenogram of the femurs, May 25, 1934.)

of the liver and elevating the diaphragm. Pyelograms showed shifting of the pelvis in one case. X-ray films of the chest, besides elevation of the diaphragm, may show metastases in the lungs. However, pulmonary metastases or involvement of the mediastinum by nodular masses is rare.

Differential Diagnosis.—In the present series of cases the primary tumor produced no characteristic clinical findings, and diagnosis depended upon the extent and distribution of metastases and the absence

of response to irradiation. The occurrence of the condition in the majority of the cases, before the age of five years, limits the number of conditions to be considered.

In the majority of cases an abdominal mass in the region of the liver or kidney is outstanding. Mesenteric cysts present anteriorly and more often occupy the midline. The degree of fixation observed in neuroblastoma is rarely present in these benign growths. Wilms' embryoma of the kidney is more frequent in children after two years of age, whereas the majority of neuroblastomas are in younger patients. Both types of tumor, however, are retroperitoneal in location and produce a large abdominal mass, accompanied by digestive com-

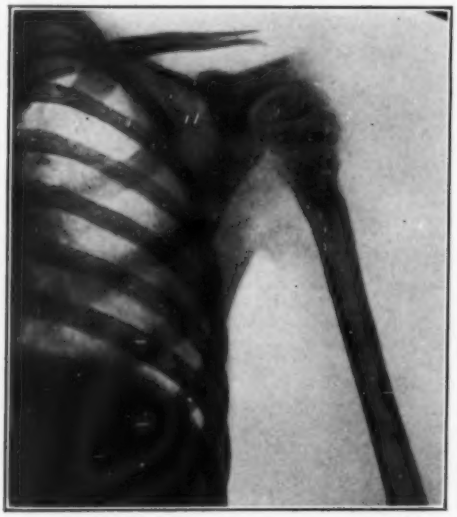

Fig. 8.—(H. L. H. 55657. Case 3.) Roentgenogram of the humerus, May 25, 1934, showing the wedge-shaped involvement behind the epiphyseal line characteristic of neuroblastoma.

plaints or fever. Hematuria, urinary obstruction, and positive findings in the pyelogram are more common in Wilms' tumors. Neuroblastoma fails to respond to deep x-ray therapy, whereas shrinkage in the Wilms' tumor under this type of treatment is fairly rapid. The varied findings accompanying widespread metastases in neuroblastoma are not found in cases of Wilms' tumor.

Neuroblastoma of the adrenal often metastasizes to the retroperitoneal lymph nodes. Primary lymphosarcoma occurring in these nodes is more common in adults. In twelve cases of retroperitoneal lymphosarcoma recorded in this laboratory, only one was observed in a child. The others were in patients varying from fifteen to sixty-two years of age. Ascites is more common in such cases of lymphosarcoma. The

superficial lymph nodes are often involved and may be biopsied to establish the nature of the tumor. In lymphosarcoma there is rapid response to irradiation, which is not found in neuroblastoma.

Ovarian tumors and sex cell rests in the retroperitoneal spaces are rare, particularly in children. They are accompanied by changes in the secondary sexual characters with precocity or pseudohermaphroditism. An Aschheim-Zondek test performed on the urine in such cases will usually give a positive number one reaction. Large ovarian tumors are freely movable, grow out of the pelvis, and are palpated in front of the colon rather than retroperitoneally.

Anemia, weakness, and unexplained fever in patients with neuroblastoma may suggest a diagnosis of leucemia. In leucemia of children with bone involvement the total white cell count may remain low, but there is usually a relative lymphocytosis.

Rheumatic fever or appendicitis was suspected early in the course of several of our cases. It is difficult to rule out these conditions early in the disease when no tumor is palpable in the region of the liver or adrenal. In the absence of cardiac findings when rheumatic fever is suspected, and in the absence of rigidity or a mass in the region of the appendix when the latter diagnosis is considered, more thorough x-ray studies of the abdomen, skeleton, and kidneys may prove of value.

When bone involvement is found by x-ray examination, a number of conditions must be borne in mind. Christian-Schüller's syndrome, chloroma, leucemia, Ewing's sarcoma and Wilms' tumor of the kidney must be considered.

In Christian's disease there are usually large circular defects in the skull or flat bones which respond to irradiation. The patients are usually older (from three to ten years), and soft-part tumors are palpable over the bones. Chloroma is most often found near puberty. Exophthalmos and lesions in the bones of the orbit may simulate the findings of neuroblastoma of the Hutchinson type. Involvement of the other bones often shows a more definite periosteal reaction with palpable tumors in the soft parts. Tumors may also be found in the oral cavity or in the paranasal sinuses. In addition, there are the general signs and symptoms of leucemia and a positive response on the part of the tumor to irradiation. Lymphoid leucemia in children (in our experience), usually of the aleucemic lymphatic type, may show bone involvement which may be indistinguishable in the roentgenogram from neuroblastoma. The enlargement of the liver and spleen has been referred to above in diagnosing the abdominal mass. The response to irradiation and a differential count of the white blood cells are important in making the diagnosis.

Ewing's sarcoma of bone is not uncommon in children after the age of four. It is rarely reported earlier. It is most common in the long

bones in which it produces longitudinal periosteal reaction with splitting of the subperiosteal and cortical layers in so-called onion-peel fashion. Involvement of other bones is seen only in terminal stages when metastases to the skull may occur. In such instances the skull involvement is accompanied by soft-part tumors underlying the bony lesions. These masses respond readily to irradiation.

Wilms' tumor of the kidney with bone involvement is extremely rare. In such cases the pelvis is usually eroded by direct extension, and the area of bone destruction is much larger than the metastatic foci seen in neuroblastoma.

PATHOLOGY OF NEUROBLASTOMA

The tumor mass was solid (often with cystic areas) and had a maximum dimension varying from 5 to 15 cm. in our series of cases. Encapsulation of the local growth was the rule, the kidney on the affected side being compressed rather than invaded. The affected adrenal was often entirely displaced by the tumor mass. In one case the kidney was practically replaced in a similar fashion, and in two additional cases the opposite adrenal. Metastasis to the retroperitoneal lymph nodes was more common than involvement of either the bones or the liver. In two instances the mesenteric lymph nodes were invaded. The occurrence of ascites has already been mentioned.

It is important to recall that neuroblastomas arise from undifferentiated cells of the sympathetic nervous system and therefore are not necessarily confined to the adrenal medulla. Similar tumors may arise in the vertebral ganglia of the sympathetic nervous system and in the paraganglia of the renal plexus in the retroperitoneal spaces. In one of our cases the tumor apparently arose in the sympathetic plexus just outside the adrenal in this manner and invaded the kidney. Normal adrenals at autopsy therefore do not rule out the possibility of malignant neuroblastoma arising in the retroperitoneal spaces.

Most of the case reports in the literature emphasize the histopathology of these tumors, detailing the relationship of the tumor cells to the normal neural elements of the sympathetic system. The majority of the neuroblastomas are uniform in structure, being composed of extremely small cells with hyperchromatic nuclei and a scarce amount of cytoplasm. The cells were often clumped or grouped, but the formation of rosettes, produced by a circular arrangement of cells with cell processes extending toward a center of the circle (so often referred to in the literature), was found in but one-third of our cases. In about one-half of the cases collected by Wahl[10] from the literature typical rosettes were found. The so-called pseudorosette (concentric grouping about capillaries) is not conspicuous in these growths.

The small cells referred to under a wide variety of names (lymphocytoid cells, neuroblasts, neurocytes, sympathicoblasts, and sympathi-

gonia) predominate in all cases in which the tumor occurs in infancy (Fig. 9). Among these small cells are larger round cells with a more vesicular nucleus and spindle cells of a carrot or pear shape resembling tumor suggest an origin from the indifferent building cells of the

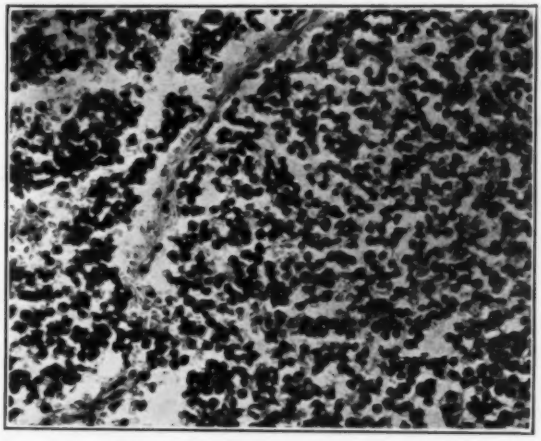

Fig. 9.—(H. L. H. 47017. Case 5.) Photomicrograph showing the characteristic histology of neuroblastoma of the adrenal in infants. The nuclei are dense with little or no visible cytoplasm. The patient was a colored male, aged two years, with a large, hard abdominal mass on the left. Autopsy revealed a neuroblastoma of the left adrenal, metastasizing to the liver, lungs, and retroperitoneal nodes. Ascites was present.

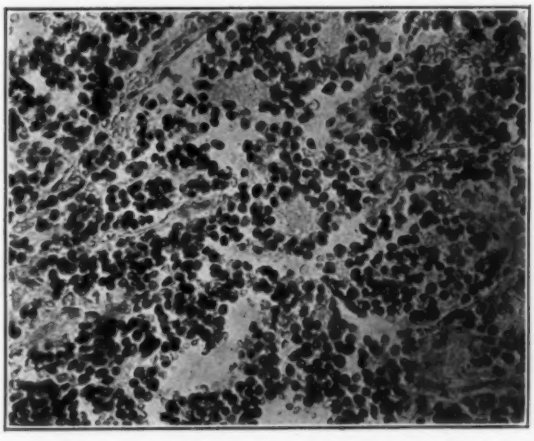

Fig. 10.—(H. L. H. 79311. Case 1.) Photomicrograph of neuroblastoma of the adrenal showing rosette formation.

young spongioblasts. These more or less constant elements of the sympathetic nervous system, with a gradual differentiation toward the more adult forms of ganglion or chromaffin cells. The larger ganglion cells or chromaffin cells seen in benign ganglioneuromas or

paragangliomas have been described in neuroblastomas but are rare. Masses of glialike fibers have also been described, but the latter were not observed in our series.

It is generally assumed that the degree of differentiation which the tumor shows on histologic examination varies with the age of the patient, but this is only relatively true. In six cases of neuroblastoma occurring in adults examined by one of us (C. F. G.[11]), only two showed adult cells in significant numbers. The other four showed cells with the same immature structure typical of the neuroblastomas occurring in infants.

The recognition of neuroblastoma under the microscope may be exceedingly difficult at times. Lymphosarcoma (or foci in lymphatic leucemia) and embryoma of the kidney of the Wilms' type cannot always be ruled out by the examination of a single microscopic section. If tubule formation of the embryonic type is seen or if muscle, cartilage, or bone is found, it can be definitely stated that a Wilms' tumor is present. If definite rosettes are formed with faint fibrillae directed toward their center, in a tumor composed of minute cells with dense nuclei, the diagnosis of neuroblastoma is more nearly certain. In lymphosarcoma and in lymphatic leucemia, Wright or Wilson's blood stains may show granules in the cytoplasm of the larger lymphoblasts with the oil immersion lens.

The primitive nature of the neuroblasts, their relationship to similar normal cells in the developing neural tube, and their rôle in the tumor process referred to as neuroblastoma are substantiated by the embryologic studies. Wright (Figs. 3 and 12) and Lehman (Fig. 16) have shown the microscopic similarity of the embryonic neuroblasts and the corresponding cells in neuroblastoma. The pleuripotentiality for further development of adult neural structures seen in these tumors indicate the close relationship of the tumor to the preexisting foci of embryonic development in the sympathetic structures where they occur. The fact that the neuroblastomas in infancy and later childhood may show more mature elements of a chromaffin or ganglionic type emphasizes these potentialities. Moreover, such, when they do occur in the tumor, correspond in type and in their order of appearance with the normal form and sequence seen in the histogenesis of these sympathetic structures.

CLINICAL COURSE AND TREATMENT

The usual clinical course for neuroblastoma is progressive with rapidly fatal termination. The average duration of symptoms before observation in our series was six months although one-half of the patients had symptoms of one month or less and in one case the lesions were observed at birth. In nearly half of the cases death followed surgical intervention within a month. A fair proportion of the cases of neuro-

blastoma, therefore, occurring in children, may run their entire clinical course, terminating fatally within the period of two months. Although softening and apparent shrinkage of the tumor mass may follow irradiation with x-rays or radium, this form of treatment in the cases observed by us did not seem to alter the speed of metastases. Surgical intervention in the present series was equally ineffective. There is one outstanding exception in the literature. This is a case reported by Lehman in 1917, and after operation in 1916. The tumor was pathologically a typical neuroblastoma of the adrenal. The patient has been reported well in 1931, fifteen years later, following complete excision of the newgrowth.

CASE REPORTS

CASE 1.—(H. L. H., No. 79311) D. C., a colored female aged sixteen months, was admitted to the hospital Sept. 6, 1932, with a complaint of an enlarged abdomen and a mass on the left side. The family history was negative. The birth had been normal. In the past history there had been otitis media at the age of four months. The present illness dated from one month before admission when it was noted that the child had a dark and strongly odorous urine. Three weeks later the enlargement in the abdomen could be seen and felt. Physical examination showed an undernourished child with pale mucous membranes. The cervical nodes were palpable. The abdomen showed a mass on the left side originating in the flank and extending beyond the umbilicus. The laboratory examination showed hemoglobin 48 per cent, red blood count 3,400,000, and white cell count 7,920. The Wassermann and tuberculin tests were negative. The temperature ranged from 99° to 104° F. The pyelogram showed the left renal pelvis shifted downward and inward and distorted in outline.

A course of five radium treatments was given, the tumor shrinking somewhat in size.

Operation was performed Oct. 26, 1932, six weeks after admission. A firm tumor with cystic areas, the size of a grapefruit, was dissected free from the capsule of the kidney. The retroperitoneal glands were enlarged. Five days postoperatively the patient died of pneumonia accompanied by otitis media. Autopsy disclosed a neuroblastoma of the left adrenal with metastases to the retroperitoneal and mediastinal lymph nodes.

CASE 2.—(H. L. H., No. 67751) M. M., a white female aged four years, was admitted to the hospital July 14, 1930, after the accidental discovery of an abdominal tumor. The family and past histories were irrelevant. The birth had been normal. The present illness showed no symptoms except the presence of an abdominal mass discovered two weeks previously. The physical examination showed an asymmetrical development, the right arm and the right leg each being over 1 cm. longer than the corresponding extremity on the left. A large mass, which was firm and nodular, was present in the abdomen extending to the umbilicus. There was general enlargement of the lymph nodes. The laboratory examination disclosed hemoglobin, 95 per cent; red blood cells 5,150,000, white blood count 15,350, negative urine, and the temperature ranging between 100° and 101° F. X-rays of the bones of the extremities were negative.

Exploratory laparotomy, performed July 19, 1930, revealed an inoperable tumor arising in the region of the left kidney. Tissue taken for biopsy disclosed a neuroblastoma of the adrenal. The child died at home. No autopsy was performed.

CASE 3.—(H. L. H., No. 55657) C. S., a white female aged five years (a normal delivery of normal parents), was admitted to the hospital Mar. 4, 1932. She had suffered from tonsillitis regularly since one year of age. She had occasional colds in the head followed by mucopurulent nasal discharge. The past history revealed that three months prior to admission the child had pain in the region of the stomach accompanied by nausea and had vomited several times. She had headaches and a low fever, which continued up to the time of admission. There were indefinite joint manifestations and pain about the left hip. The child was restless at night and had lost her appetite. She had a temperature of about 101° F. at admission and was thought to be subject to rheumatic fever. The physical examination showed pallor and weakness. She could not raise herself to a sitting position. She was lying without complaining of extreme pain but objected to being moved. Her eyes were negative to all examinations on admission. The lymph nodes were palpable in the cervical region, in both axillae, and in the groin. There was marked muscle spasm of the abdominal muscles, but no masses were felt. On motion the child complained of pain in the group of muscles in the region of the knee and also pain about the left hip. No bone tenderness, however, was noted.

Laboratory examination showed hemoglobin, 62.5 per cent; red blood count, 3,920,000; white blood count, 8,050; and temperature, 101° F. Examination of the spinal fluid was negative. The blood Wassermann test was negative. The Widal reaction was negative. The blood chemistry showed nonprotein nitrogen, 22 mg. per cent; cholesterol, 219 mg.; protein, 6.21 gm. per cent; albumin, globular ratio, 1.8.

The x-rays showed changes in the upper end of shaft of the left femur, suggesting osteomyelitis. Subsequently the roentgenograms of the bones showed multiple areas of rarefaction in the upper femur and humeri, in the pelvis, and in the skull (Figs. 3 to 8).

When the child had been in the hospital about a month and a half, it was noticed that the right eye became swollen and puffy and the regional lymph nodes enlarged.

Since the bones about the left orbit seemed definitely involved, a biopsy was done on May 27, 1932, in this region. The diagnosis of neuroblastoma was made from the frozen section and confirmed by subsequent study. The child died at home about eight months after the onset of her symptoms. Autopsy was not performed.

CASE 4.—(H. L. H., 52545) H. B., a colored male nine years of age, was admitted to the hospital Mar. 14, 1927. The family history was negative, the birth, normal. Measles occurred at the age of six years, and whooping cough and chickenpox, at the age of seven years. The present illness dated from three weeks before admission, when the child began to be less active and to lose his appetite. One week later a mass, which was increasing rapidly, was noticed in the epigastrium. There was occasional nausea and vomiting. The physical examination showed a fairly well-nourished child with evidence of recent loss of weight. The thyroid gland was enlarged and nodular. Over the heart a diastolic murmur was heard. The mass in the abdomen showed two rounded projections in the upper and middle portion. Rectal examination revealed a lump palpable along the inner rectal wall. The laboratory examination showed hemoglobin, 48 per cent and white blood count, 13,000. The urine showed albumin and a few red blood cells. The temperature ranged from 99° to 100° F. The blood chemistry showed a retention of nonprotein nitrogen.

The mass was explored on Mar. 25, 1927. The child died shortly thereafter. At autopsy a neuroblastoma, originating in the right adrenal with metastases to

both kidneys, heart, lung, liver, left adrenal, pancreas, prostate, thyroid, ureter, bone marrow and skin was found. Although the bone marrow at autopsy showed tumor metastases, the x-rays of the skeleton taken during life were pronounced negative.

CASE 5.—(H. L. H., 47017) B. G., a colored male aged two years, was admitted to the hospital Nov. 24, 1925. The family history was negative, the birth, normal. The patient was the result of a third pregnancy and had been breast fed for eighteen months. His parents described him as being always sickly and having frequent attacks of bronchitis and colds. The present illness dates from two months before his admission. He began losing weight; his appetite was very poor; and he was very restless at nights. He had been feverish off and on during this interval. Physical examination showed a very poorly nourished and underdeveloped colored boy crying with pain. On the left side of the abdomen there was a large, hard, smooth mass. His spleen was also enlarged. Laboratory examination showed hemoglobin, 30 per cent; white blood count, 20,000. The temperature ranged between 102° and 104° F.

The operation, performed on Dec. 11, 1925, disclosed a large, inoperable tumor in the region of the kidney. The child died two and one-half months after admission and four and one-half months after onset of symptoms. The autopsy revealed a neuroblastoma in the left adrenal region involving the left kidney, with metastases to the liver, left lung, and retroperitoneal nodes. The primary mass was very vascular, soft, and cystic. Ascites was present.

CASE 6.—(H. L. H., No. 42879) E. O. B., a white male sixteen months of age, was admitted to the hospital Dec. 29, 1924. His family history was negative, birth normal. The past history was negative. Three weeks before admission the child developed a cough followed by loss of appetite and loss of weight. A mass appeared in the region of the stomach two weeks later, and a mass in the neck and left side the next day. The child seemed feverish. Physical examination showed a pale boy with enlarged cervical, axillary, and inguinal glands. In the abdomen on the left side there was an irregular mass. There were several small masses superficial to the large mass. The x-ray of the extremities showed areas of resorption in the upper femur and fibula, the lower end of the right radius, and in the upper part of the humeri. The laboratory examination showed hemoglobin, 33 per cent, and white blood count, 23,400. The temperature ranged from 100° to 102° F.

The patient died on Jan. 15, 1925, six weeks after the onset of symptoms. Autopsy showed a neuroblastoma arising from the left adrenal. The tumor had metastasized to the right adrenal, retroperitoneal nodes, and liver.

CASE 7.—(H. L. H., 32539) R. D., a white male twenty-three months of age, was admitted to the hospital Mar. 22, 1922. The family history was negative, the birth, normal. The past illness dated from one month before admission, when the child began complaining of pain in the abdomen. He vomited several times and had a fever. After a lapse of ten days, at which time he seemed well, he had another attack similar to the first. Physical examination showed a pale restless child with a markedly distended abdomen. The right flank bulged more than the left. Palpation showed a hard, smooth mass in the right abdomen, which did not seem painful or tender. The laboratory examination showed hemoglobin, 40 per cent; white blood count, 16,600; and temperature, 100° F.

Operation was performed on June 5, 1922. The child died the next day. Autopsy showed a neuroblastoma of the right adrenal extending into the liver with metastases to the mesenteric, retroperitoneal, and mediastinal lymph nodes.

CASE 8.—(H. L. H., No. 4119) L. K., a white male one year of age, was admitted to the hospital in March, 1914. The child had had diphtheria and measles at the age of nine months and since that time, a discharge from the nose and both ears. The present illness dated from a few days before admission, when the child began vomiting. Physical examination showed a well-developed pale child with a markedly distended abdomen. The breathing was rapid and difficult. Examination of the abdomen showed marked rigidity of the right side and a definite mass extending from the crest of the ilium to the costal margin. In the right axillary line there was a second mass springing from the region of the kidney. Laboratory examination showed hemoglobin, 45 per cent, and white blood count, 21,300. The temperature ranged between 103° and 106° F.

Operation, performed Apr. 30, 1914, disclosed a mass occupying the right kidney region. The child died shortly after the operation. Autopsy showed a neuroblastoma of the right adrenal with invasion of the regional lymph nodes.

CASE 9.—(H. L. H. 39467) H. K., a white male three years of age, was admitted to the hospital July 5, 1927. The present illness dates to a few weeks before admission, when the child vomited several times. A lump was noticed on the right side of the abdomen at this time. Physical examination was negative except for the mass on the right side, which occupied the entire right lower quadrant. Laboratory examination showed hemoglobin, 60 per cent, and white blood count, 21,000. The temperature ranged between 101° and 103° F.

Operation was performed July 6, 1927. Because of the location of the mass and the fever and leucocyte count, an appendiceal abscess was suspected and the abdomen was opened through a McBurney incision. An inoperable tumor was found to be present. Tissue removed showed a neuroblastoma apparently in the region of the right adrenal. The child died shortly afterward.

CASE 10.—(H. L. H. 42917) M. H., a white female aged three weeks, was admitted to the hospital Jan. 5, 1925. The family history was negative; birth was normal. From birth the child appeared very drowsy and did not cry as much as other children. She nursed poorly. She had diarrhea and vomited occasionally. At the age of one week the mother noticed that the child had a large abdomen. This had been growing progressively larger. Physical examination showed a large abdomen with dilatation of the superficial veins. The liver was very much enlarged. The temperature was 102° F. Laboratory examination showed hemoglobin, 68 per cent; and white blood count, 19,600. The differential count showed polymorphs, 50 per cent; lymphocytes, 42 per cent; and myelocytes, 8 per cent. The blood Wassermann reaction was negative, and the urine was negative.

The child was treated with irradiation, 2 gm. of teleradium being used. The child died soon after admission with terminal pneumonia. Examination at autopsy showed a mass in the neighborhood of the left adrenal with metastases to the right adrenal. The liver showed numerous metastases also.

CASE 11.—(H. L. H., 79043) D. C., a white male aged three years, was admitted to the hospital Aug. 12, 1932. The family history was negative; birth was by forceps. The present illness began about six months before admission to the hospital, when it was noticed that the child limped on the left leg. In addition, there was an apparent fever and a vague pain in the other extremity. Five months later a prominence of both eyes was noted, the left being worse than the right with a discoloration of the eyelids. He became progressively more anemic. Physical examination showed a pale child. The veins on the forehead were very prominent, and there was a positive Macewen sign. The neck was stiff. The left eye protruded from the socket. The right eye also bulged markedly. The lids were blue and discolored. No masses could be felt in the abdomen. The x-rays showed a moth-eaten

appearance of all the bones. The laboratory examination showed hemoglobin, 45 per cent; red blood count, 2,050,000; and white blood count, 7,800.

The child died at home Oct. 26, 1932, eight months after the onset of the disease. Autopsy was not performed.

CASE 12.—(J. H. H. 13336) B. M., a colored female eighteen months of age was admitted to the medical service with a large mass in the left hypochondrium extending from the umbilicus into the lumbar region. The mother knew of no previous symptoms. The mass was painful to palpation. Laboratory examination showed red blood count, 3,600,000 and white blood count, 18,666. The temperature was 99.6° F. Death was sudden on Aug. 28, 1901 with a terminal rise of temperature.

The autopsy showed the left side of the peritoneal cavity filled by a tumor mass which was pushing the descending colon to the midline. There were metastases in the left lung and in the liver. The liver measured 14 x 8 x 5 cm. The left ureter could be traced only 3 cm. upward and was lost in the tumor mass. The left kidney and adrenal were entirely replaced by the tumor. The tumor was soft and fluctuant and had a lobular and cystic appearance. On section a semifluid, gelatinous material poured forth from various necrotic areas. The microscopic diagnosis was neuroblastoma of the adrenal.

CASE 13.—(P. N. 43518. Referred by Dr. Boulware.) The patient was a white male aged thirteen years, who had received a blow to the right side of his abdomen. This was followed by pain of three weeks' duration in the right abdomen and right shoulder. There was dyspnea and precordial distress. The patient had a temperature of 100.6° F. On examination there was bulging of the right chest and palpable glands in both axillae. The abdomen was distended and bulging with marked tenderness on the right. The liver apparently extended down to the crest of the ilium.

A laparotomy disclosing inoperable peritoneal metastases was performed. The biopsy specimen showed a neuroblastoma apparently arising at the site of the adrenal.

CASE 14.—(P. N. 46760. Referred by Dr. E. B. Smith.) A full-term fetus was found to have a large abdominal mass. The abdomen was incised and fragments of an enlarged liver removed before the fetus could be delivered. At autopsy the abdomen was filled with a liver weighing 700 gm. and measuring 14 x 12 x 6 cm. The liver presented irregular white nodules, and the cut surface gave the appearance of granite. The right adrenal was replaced by a tumor mass measuring 6 x 6 x 5 cm. which was diagnosed neuroblastoma.

CASE 15.—(P. N. 45704. Referred by Dr. L. Keasbey.) The patient was a white male, aged four years. The mother had noticed a tumor in the upper epigastrium for one year previous to admission. Shortly after the discovery of the tumor there were attacks of recurrent vomiting and constipation. Examination showed a tall, normally developed boy with a large tumor in the epigastrium, visibly expanding the abdominal wall. The mass extended across to the right side beyond the midline to the region of the left kidney and apparently arose in the left flank. It was firm and moved with respiration.

Exploratory laparotomy disclosed a large retroperitoneal mass thought to be arising from the left kidney. The patient received high voltage x-ray therapy postoperatively over the tumor area. One-third of the full dose was given through two portals on the first day, and one-tenth of the total dose daily thereafter. The tumor grew rapidly after treatment, and three months later x-rays of bones showed involvement of the ribs, scapulae, and the upper humeri. Death occurred Dec. 19, 1931. At autopsy there was exophthalmos of both eyes; the abdominal cavity showed ascites and studding of the peritoneum by tumor metastases. A mass 15 × 17 cm. originating at the site of the left adrenal was found in the retroperitoneal spaces.

The left kidney was not involved. The right adrenal was encased in the tumor as was the right kidney. The tumor mass also extended about the pancreas. There were metastases in the liver, the clavicle, ribs, skull, and humeri, also in the lungs and about the lower mediastinum.

CASE 16.—(P. N. 46774. Referred by Dr. Lindsay.) The patient was a colored male, aged two months, without any significant early history except cough and nasal discharge and recent diarrhea. The patient was admitted because of the acute abdominal condition. Examination showed a greatly distended abdomen in which a mass could be palpated across the abdomen and extending well below the umbilicus. Exploratory laparotomy disclosed a tremendously enlarged and nodular liver, the seat of extensive metastases. The patient died postoperatively of pneumococci meningitis. Autopsy showed a neuroblastoma of the left adrenal, dark red in color, 4 cm. in diameter. The liver weighed 870 gm. and was filled with metastases.

CASE 17.—(P. N. 49528. Referred by Dr. Bruck.) The patient was a white male, aged six years, without a significant past history. Two months previously there had been pain in the lower flank with marked vomiting followed by constipation. He was admitted to another hospital where a diagnosis of a retroperitoneal tumor was made. He returned home and was then admitted to another institution. Apparently at the time of the second admission, there was marked loss of weight, anemia, and definite metastases. In September, 1932, three months after the onset of the illness, he was admitted to a third hospital. At this time his condition was practically moribund. Examination revealed enlargement of all the regional lymph nodes. There was marked pallor and an anemia of the secondary type and a moderate leucocytosis. X-ray examination showed a large mass in the upper mediastinum and mutiple foci of bone resorption of small size in nearly all the bones. The patient died a few weeks after admission.

At autopsy there was a tremendous retroperitoneal mass occupying the region of the right kidney and obstructing the right ureter. Both adrenals were normal. There were metastases to the retroperitoneal glands. The left lung was collapsed. There was a large mass arising from the mediastinum and obstructing the left bronchus. There was definite involvement of the bones. The microscopic diagnosis was neuroblastoma arising in the retroperitoneal spaces.

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SEMEN ALLERGY IN CHILDREN

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IN THE past sixteen months three children, allergic to seminal fluid, have come to the writer's attention. Of a total of eighty-four suspected cases of protein hypersensitiveness, nineteen positive cases were found by making skin sensitization tests, three of which were specific for semen. If we consider these three cases on a basis of a representative proportion, then the relatively high prevalence of this type of allergy is 15.8 per cent of the positive (nineteen) cases. It would be well, therefore, to bear its existence in mind, especially in the face of its elusive history or presentation of an etiological factor, together with the diversified clinical symptoms which further complicate the picture and make diagnosis difficult.

Duke,[1] in referring to the compatibility between the blood of patients and donors so far as agglutinins are concerned, says: "If individuals can be sensitive to the blood of other individuals, it seems quite likely that they could be sensitive to other body fluids or secretions and might react upon intimate contact. This type of sensitiveness, no doubt, exists but must be quite rare."

In following the three cases, it will be noticed that the uncovering of their etiologic factors was more or less accidental. The semen protein used in making the skin sensitization tests was a specimen collected from an unconcerned adult who desired examination of his spermatozoa for motility. The semen was prepared for use by dessication and grinding.

CASE 1.—A female patient, aged six years, was referred for skin sensitization tests. Her physician accompanied the parents and in giving the history incidental to the case mentioned the fact that the attacks were periodic. The father interrupted and stated it was more or less of a constant nature. The mother on the other hand agreed with the doctor in the argument. Upon further inquiry, it was found that the child was in the habit of climbing into her mother's bed almost daily and continued this practice even after both parents had occupied the bed. The father, a traveling man, would come in at periodic intervals and invariably notice the child beginning to ail; usually about the second day of his stay at home. Although the rhinologic examinations were negative, as was the respiratory tract, the child would develop a marked coryza, and from six to twelve hours later an urticaria would develop of a rather marked intensity. All the group protein reactions were later found to be negative. It now became evident that to the father it appeared that the child was ill constantly. The consistent relation of the child's illness with the father's home-coming served as a clue to the solution. On physical examination the extremities and abdomen, although markedly involved, showed no distinctive skin lesions aside from edema and mild erythema; the intense itching caused the patient

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to resort to vigorous scratching thereby masking all diagnostic features of the skin lesions. The semen test protein was applied to the arm by the cutaneous scratch test and within twenty-four hours showed a diagnostically positive wheal increased to about 8 diameters around the original 2 mm. diameter of the scarifying site.

CASE 2.—A male patient, aged nine and one-half years, son of a farmer, was referred for skin sensitization tests. Although it was the cold time of the year, the physician felt that the pronounced "asthmatic" attacks were of a pollen-sensitive nature. The patient complained of abdominal distress which was not relieved by the usual treatment measures for "indigestion" and more recently thought he had pediculosis pubis. Aside from the excessive lacrimation, examination of the head was negative. The patient ate well and of everything, but in spite of his good appetite he was losing weight and became "nervous and fidgety." There was no recollection on the part of the parents of his being affected by any particular foodstuff or in any special environment. Skin tests were entirely negative to all pollens endemic to this region. The semen protein reaction, which has now been included in the armamentarium (since the advent of Case 1) showed a widespread eczematous reaction around the site of the inoculation, to almost cover the lateral aspect of the arm. A generalized itching was the complaint of most annoyance to the patient. With these findings the etiologic contact was sought, and it was finally found that the patient would don a pair of old overalls in place of his shirt and trousers, while working in the woodshed; these overalls showed on each side of the fly an area of small crusts which upon examination proved to be dried semen. The troublesome region was consistent with the level of his upper and central pubic area. The itch there, no doubt, is what was interpreted as pediculosis.

CASE 3.—The patient, a fourteen-year-old boy, was referred for skin sensitization tests. Special attention was to be given to protein materials comprising the articles of clothing. The physician was suspicious of wool allergy or the clothing dyes. This patient wore the so-called red flannel underwear. He presented large faintly reddened areas on each thigh, with that of the left side about twice the cross diameters of the contralateral side. They occupied the anterior portion of both thighs and extended laterally around. The lesions were not distinctive of any definite skin disease. Aside from the pruritis, the involved area showed an occasional deep-seated, fine papule; the rest of the lesion appeared to be a specifically produced erythema which has recently been described by Wheeler.[2] It appeared like an old ink blotch with a circumscribed area which stood out demarcated from the adjacent uninvolved skin. It was practically a uniformly distributed lesion except for the previously described papules. There were no general symptoms. The skin tests revealed moderately positive reaction to the cheese group; all other groups, including the textile materials and cellulose, were negative. The patient reported to the laboratory for the readings of the tests the following day but did not wear the "Sunday clothes" in which he appeared the previous day. Upon lowering his trousers to reexamine the lesion, the characteristic odor of semen was noticed. It was apparent that there existed an intermittent spermatorrhea. Upon questioning he admitted playing with his penis, by pulling it over to one side or the other through the trousers pockets. He had been in the habit of doing this for the past six months. The duration of the complaint was about six months. The semen protein skin test disclosed a massive positive reaction the following day while the wheal of the cheese group was already beginning to fade.

The interesting feature of Case 3 was hypersensitivity to an autogenous body fluid.

The question next arose whether it was possible to prepare desensitizing semen antigens for the patients in Cases 1 and 2. In the face

of the more recent work[3, 4] of inducing sterility, both of transient and permanent nature, with semen inoculations, and inasmuch as the effect of the inoculations in children when they reach maturity is a phase which apparently has not been fully studied at this writing, the writer advised against its use. The cases of semen allergy seem to respond very favorably to proper hygienic management, that is, avoiding contact with the fluid. This was shown by following the clinical courses of the above cases.

SUMMARY

1. Children are sensitive to seminal fluid and have varied symptoms of allergy.

2. Hypersensitivity to autogenous semen has been demonstrated.

3. Semen allergy is presented by elusive symptoms and etiology. It should therefore be regarded more commonly as a causative factor of protein sensitivity.

4. In making skin tests on children for allergy or hypersensitivity, seminal fluid protein should be included routinely in the armanentarium of test proteins.

5. Specific desensitizing antigens should not be used in treatment on account of their potentiality to cause sterility later.

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THE EPIPHYSES IN RICKETS, SYPHILIS, AND THYROID DEFICIENCY

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THE time of appearance and development of epiphyses and centers of ossification has been a subject of widespread investigation and study by many workers. Engelbach has laid particular stress upon his belief that late appearance of epiphyses and centers of ossification represents an essential criterion in the diagnosis of congenital thyroid

Fig. 1.—Rickets and syphilis in a nine-month-old infant. Early appearance of the epiphyses. The capitellum and the distal epiphysis of the radius normally appear in the second year of life.

deficiency, and he devotes the greater part of one volume of his *Endocrine Medicine* to this feature in the osseous system.

Textbooks on pediatrics make only slight mention of this phase of diagnosis in congenital hypothyroidism, probably because clinical rec-

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Fig. 2.

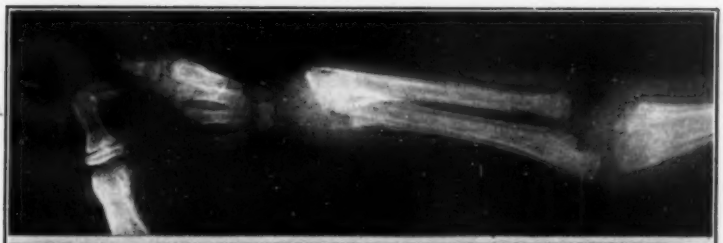

Fig. 3

Fig. 4

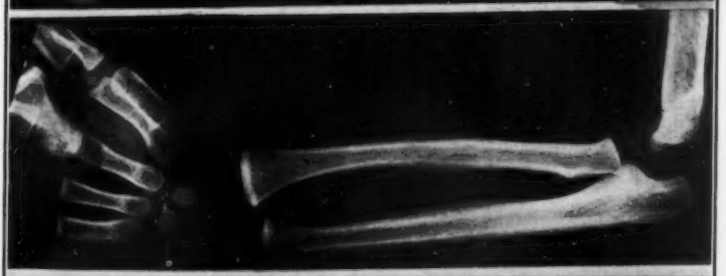

Fig. 5.

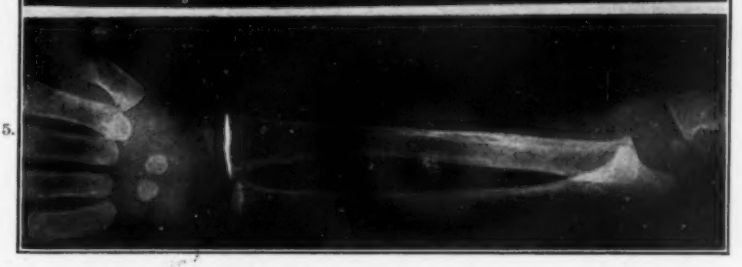

Fig. 2.—Syphilis in an infant, aged two months. Early appearance of the capitate and hamate bones, which normally appear between the sixth and eighth months.

Fig. 3.—Syphilis in a patient, six months old. Normal appearance of the centers of ossification.

Fig. 4.—Syphilis in a patient, aged sixteen months. Early appearance of the epiphyses of the metacarpals and phalanges, which normally appear in the third year of life.

Fig. 5.—Rickets in a one-year-old patient. Early appearance of the capitellum and distal epiphysis of the radius, which normally appear in the second year of life.

ognition of well-defined cases of cretinism is not difficult. Mild cases of hypothyroidism are impossible to diagnose by available clinical standards, and it is in these cases that a study of the epiphyses becomes of practical value, for without exception they exhibit a variable delay in the time of appearance and development.

Various authors describe this phenomenon as being representative of other diseases. Engelbach[1] states that "scurvy, rickets, and osteogenesis imperfecta exhibit a retardation in the appearance, union, and

Fig. 6. Fig. 7. Fig. 8.

Fig. 6.—Rickets in an infant, ten months old. Early appearance of the distal epiphysis of the radius and capitellum, which normally appear in the second year of life.

Fig. 7.—Rickets in a three-year-old child. Normal appearance of the epiphyses and centers of ossification.

Fig. 8.—Rickets in a child, aged four years. Normal appearance of the epiphyses and centers of ossification.

development of the centers of ossification." Continuing he says, "A deviation of more than six months from the normal, as shown by an absence of centers or union of epiphyses which should be present at a given age, is positive evidence of thyroid inactivity providing simu-

Fig. 10.

Fig. 9.—Hypothyroidism in a child, aged twenty-two months. At this time there should be present in addition to the carpal bones, the capitellum and distal epiphysis of the radius.

Fig. 10.—Hypothyroidism in a twelve-year-old child. At this age the centers should be much more developed. The pisiform and the distal epiphysis of the ulna should be present. The former normally appears in the twelfth year, and the latter, in the sixth year of life.

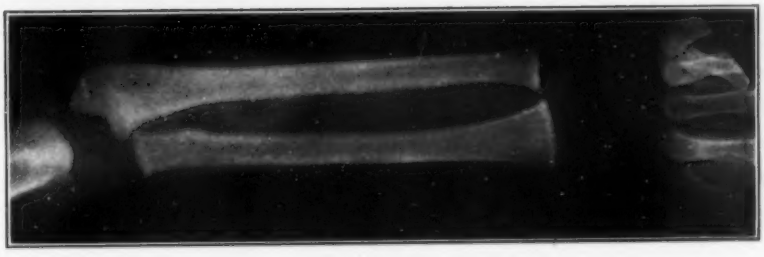

Fig. 9.

lating disease (rickets, scurvy, hereditary lues) can be excluded." Plaut[2] found a delay in the appearance and a decalcification of the carpal centers in cases of rickets. Goldberger and Mellin[3] found that the appearance of carpal centers in infants with rickets was delayed as compared with infants free from rickets. Hess[4] says that in rickets the development of carpal centers "may be delayed."

Because our observations have failed to demonstrate this phenomenon in the same light, we have undertaken an analysis of our findings in a series of cases. This study will show that syphilis, rickets, and scurvy exhibit a normal, and often an early appearance of epiphyses and centers of ossification, and we feel, therefore, that attention should be directed to this fact in order that the prevailing apparent confusion might be clarified.

In our series we undertook a study of epiphyses in 71 cases of congenital syphilis and 56 cases of rickets. As a criterion of the normal osseous development, we studied the standards of Engelbach, Metjer and Waters, Knox, Rotch, Poland, Cohn, and Allen.[5] The standards of Cohn and Engelbach agreed more closely than those of the other workers and therefore were used as the criterion by us. Our observations appear to bear out their apparent correctness.

In the 56 cases of rickets 10 showed early appearance and 46 normal appearance of the epiphyses and centers of ossification; of the 71 cases of congenital syphilis, 28 showed early appearance and 43 showed normal appearance of the epiphyses and centers of ossification. Our observations with cases of scurvy and ostogenesis imperfecta are similar to the above mentioned findings, but the cases studied are too few to permit the drawing of conclusions.

The data secured in our series of observations convince us that late appearance of epiphyses or centers of ossification cannot be attributed to syphilis or rickets; however, they rather clearly indicate that these findings may well be considered diagnostic of congenital thyroid deficiency. Radiologic pictures of ten of our cases are given here to permit opportunity for first-hand observation by the reader. These pictures represent a cross-section of our series.

It will be noted that the appearance of epiphyses and centers of ossification present striking uniformity and logically point to the conclusions above stated.

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3. Goldberger and Mellin quoted by Hess, A.: Rickets, Osteomalacia and Tetany, Philadelphia, 1929, Lea & Febiger, p. 265.
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PRIMARY PERITONITIS IN CHILDREN

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PRIMARY PERITONITIS, although comparatively uncommon, is not a rare condition in children. The incidence is variously given by different authors. Barber[1] and McCartney and Fraser[2] stated that it constitutes about 2 per cent of abdominal emergencies in childhood; Lipshutz and Lowenburg[3] gave the incidence as 10 per cent; Ottenheimer[4] gave a lower incidence, 1 to 2 per cent. Of 2,200 general surgical admissions in children in a ten-year period, we encountered eleven cases, or one-half of 1 per cent.

It is the uniformly high mortality rate which has led to the extensive study of this disease. Lipshutz and Lowenburg reported 100 per cent mortality in twenty-three cases. Huber's[5] mortality was from 80 to 100 per cent. Ciminata[6] in his own series of eight cases, had a 50 per cent mortality. Duncan[7] had a mortality of 68.6 per cent in his series of sixty-seven cases. Nine of our eleven patients died, a mortality rate of 75 per cent.

ETIOLOGY

The etiologic agent causing primary peritonitis is either the pneumococcus or the streptococcus. The former organism is by far the more frequent offender. Richter,[8] in the instance of the streptococcus variety, points out the relationship of epidemic streptococcus sore throat with streptococcus peritonitis. In our own cases of streptococcus peritonitis, a definite history of a preceding upper respiratory infection was obtainable in every case. There does not seem to be any seasonal relationship.

The disease occurs almost exclusively among young girls. All of our eleven cases occurred in girls, from two to ten years of age. There were five females and three males among Barber's cases. Duncan's cases were 80 per cent among girls. Ciminata's cases numbered five females and three males.

The fact that the great majority of cases occur in females has given rise to the theory that the peritoneal sac is invaded directly and primarily through the female genital tract. But this does not explain the definite occurrence of the disease in males. Anatomically, the

From the Abraham Jacobi Division for Children of the Lenox Hill Hospital, service of Dr. Jerome S. Leopold.

Read before the Lenox Hill Hospital Clinic of the Graduate Fortnight of the New York Academy of Medicine, Oct. 31, 1934.

peritoneum forms a closed sac, communicating with the outside only in the female sex through the genital tract.

How do the organisms reach and attack such a highly resistant membrane? Several explanations have been offered:

1. *Through the Genital Tract.*—This theory is strongly favored by McCartney and Fraser.[2] They point out that the nearness of the rectum to the vagina permits virulent pneumococci and streptococci present in the feces to enter the vagina. The fact that the disease affects the poorer classes of society suggests lack of cleanliness. In some cases pneumococci have been cultured from the vagina. At operation, inflammation of the fallopian tubes is occasionally encountered. This, however, is not a constant finding.

McCartney and Fraser maintain that it is not essential that a lesion of the genital tract be demonstrable in order to prove the passage of the organism. They point out the undisputable fact that the pathologic lesion in primary pneumococcus peritonitis first attacks the pelvic peritoneum. If a celiotomy is performed in the early stages of the disease, the pelvic peritoneum, both visceral and parietal, is found to be red and inflamed; the lower loops of the intestines are distended; very little fluid is encountered.

In further support of this theory, there is the universal recognition that the gonococcus invades the peritoneum through this route. On the other hand in gonococcus peritonitis, definite lesions of the genital tract are discernible.

Those who hold this route as the portal of entry deny that primary pneumococcus peritonitis can occur in boys. They feel that in males a focus must be present, though not demonstrable, in some other part of the body. This viewpoint does not seem tenable.

2. *Through the Gastrointestinal Tract.*—The pneumococcus is often present in the oral cavity. It has occasionally been found in the peritoneal cavity following the perforation of a typhoid ulcer and in cases of perforated appendicitis. Furthermore, it has also been cultured from the stool. Hence, its presence in vaginal secretions could conceivably be a contaminant.

Authors generally deny the migration of organisms through the healthy intestinal wall, but in dealing with an altered intestinal wall they all admit the possibility of the migration of the organisms. It is on this basis that we explain the peritonitis secondary to a mesenteric thrombosis or an intestinal occlusion.

When patients with peritoneal inflammation are operated upon, we see intestinal loops so congested, dilated, ecchymotic and with thinned walls, susceptible to injury by the least trauma, that it seems quite simple to admit that organisms could penetrate such a susceptible portion of altered tissue. The richness and localization of lymphatic

tissue in the ileocecal region would favor inflammation at this site, which would so alter the intestinal wall as to allow the passage of the organisms. Stoos (quoted by McCartney) has demonstrated the presence of the organism in the subperitoneal tissues of the intestinal coat, in cases of pneumococcus peritonitis.

Clinically, the localization at the ileocecal region as the portal of entry would explain the constant finding of generalized abdominal tenderness, especially marked in the right lower quadrant.

Militating against this theory of a portal of entry, there are two outstanding facts:

A. Workers have repeatedly failed to produce pneumococcus peritonitis experimentally in rabbits by feeding them large doses of virulent organisms.

B. Despite the great number of upper respiratory and pulmonary infections, in which organisms unquestionably reach the gastrointestinal tract and hence the rich lymphatic bed of the ileocecal region, the occurrence of peritonitis is comparatively rare.

3. *Through the Blood Stream.*—There are some clinicians who feel that the pneumococci reach the peritoneum directly through the blood stream. Huber[5] stated that in his opinion pneumococcus peritonitis is very often the expression of a septicemia.

It is difficult to explain the sole and primary localization of the pneumococcus in the peritoneum without affecting other sites more predisposed to the organisms, i.e., lungs, pleura, meninges, joints, bones. Blake and Cecil[9] showed that by intravenous injections of pneumococci a fatal septicemia was produced and in no case did either pneumonia or peritonitis occur. Again we have the additional knowledge that the pneumococcus can be isolated from the blood stream in practically every case of lobar pneumonia, but, according to Rolleston,[10] peritonitis secondary to pneumonia is quite rare (eleven cases out of 4,454, or 0.24 per cent).

In view of the above, is it reasonable to believe that in every case of pneumococcus peritonitis there is a focus in the pharynx or the lungs, usually undemonstrable, from which arises a bacteremia leading to infection of the peritoneum?

Thus, a positive blood culture in primary peritonitis (in many cases it is repeatedly negative) is really an expression of a septicemia *secondary* to the focus in the peritoneum, *not* the cause of the peritonitis.

4. *Through the Lymphatic Channels.*—A theory advanced, which has neither been widely nor completely accepted, is that the organisms reach the peritoneum through the lymphatic channels, secondary to a focus in the body, usually the pharynx or lungs. The lymphatic communications between the thoracic and abdominal cavities through the diaphragm are mentioned, but it must be remembered that the lym-

phatic drainage is upward from the abdomen to the thorax, rather than the reverse. Pleural complications secondary to appendicitis occur, but purulent peritonitis secondary to pneumococcus empyema has never been observed.

To admit the possibility of this route as a portal of entry is against all known facts of pathology. Furthermore, the disease is too intense and widespread for lymphatic origin.

SYMPTOMATOLOGY AND PATHOLOGY

Primary pneumococcus peritonitis has a sudden onset, with severe abdominal pain, vomiting, and fever. Diarrhea is frequently encountered. Herpes of the lips or cheeks may be present. There is usually tenderness and generalized abdominal rigidity. The former especially marked in the right lower quadrant. No history of any preceding upper respiratory infection was obtainable in seven cases of pneumococcus peritonitis.

In contrast to the above, in four cases of streptococcus peritonitis a history of an upper respiratory infection, from one to two weeks before the onset of the abdominal symptoms, was obtainable.

Primary peritonitis has really two phases or two stages:

1. *The early stage* which usually coincides with the first twenty-four hours after the onset. Operation at this stage reveals a marked congestion of both the visceral and parietal peritoneum, especially marked in the pelvic region. The ileocecal-appendiceal region is most markedly affected. At this stage, there is no frank pus, but usually some turbid fluid. Culture of this fluid may be sterile (Case 5).

2. *The late or purulent stage* at which operation reveals frank pus in the abdominal cavity. The intestinal loops are markedly inflamed, bathed in pus, and fibrin flakes. Invariably the appendix, whenever removed, was pathologically reported as acute periappendicitis.

In the most favorable cases a localization has occurred with definite walling off of the process. It is in this latter group of cases that recovery may be expected.

DIFFERENTIAL DIAGNOSIS

Besides acute appendicitis, primary pneumococcus or streptococcus peritonitis must be differentiated from lobar pneumonia with abdominal signs. In several of our cases, chest involvement was suspected. This, however, was disproved by roentgenologic examination of chest and subsequent clinical observations.

In an attempt to differentiate this condition from acute appendicitis, abdominal puncture has been used. There is no unanimity of opinion as to the safety and value of this procedure. It has been pointed out that a negative puncture does not exclude the possibility of a peri-

tonitis. Neuhof and Cohen[11] reported 100 cases in which this procedure was done without any ill effects. However, they point out the danger in cases of chronic peritonitis with possible adhesions between the visceral and parietal peritoneum.

Abdominal puncture was performed in three of our cases; from one was cultured pneumococcus, and from the others, streptococcus. Because of the positive culture, operation was withheld. It is our opinion that this procedure is practically harmless and should be adopted in every case in which the diagnosis of an abdominal condition suggests either a pneumococcal or streptococcal condition. It is only after a positive diagnosis has been made that the question arises if and when laparotomy should be performed.

TREATMENT

The treatment of primary peritonitis is unsatisfactory. In studying the reports of series of cases, one realizes that the mortality rate is the same whether or not operation is performed. In their 23 cases, Lipshutz and Lowenburg, awaiting localization, did not operate on some (20 per cent); these, as well as those operated upon, died.

If operation is decided upon, when should it be done? It is the consensus of opinion that only those cases recover that are operated upon late in the disease, or when localization has occurred. Of great significance is the constant fatal outcome following operation in the early stage of the disease. Only those cases, in which operation is delayed for one reason or another, seem to recover.

The use of sera and transfusions seem to be unavailing. In our cases the outcome was not changed either by transfusion or antipneumococcic sera.

CASE REPORTS (TABLE I)

CASE 1.—E. M., a female child two years old, was admitted on Apr. 1, 1934, with a history of pain in the abdomen, diarrhea, vomiting, and fever of three days' duration. The onset was abrupt; the child was awakened from sleep by severe abdominal pain. Her past history was essentially negative.

Physical examination revealed an acutely ill child. The pharynx was slightly congested. There was slight dullness over the left lower lung. The abdomen was tender with definite muscular spasm, especially marked in the right lower quadrant.

The white blood count was 24,750, of which 82 per cent were polymorphonuclear leucocytes. The possibility of lobar pneumonia with abdominal signs was considered.

When x-ray examination of the chest failed to reveal any signs of consolidation, a diagnosis of acute peritonitis, primary, or secondary to a ruptured appendix, was made, and operation was decided upon.

Operation was performed four days after the onset of the illness and twenty-four hours after admission to the hospital. A large amount of greenish turbid fluid was encountered in the peritoneum. The intestines were inflamed and distended. The

TABLE I

PRIMARY PERITONITIS

CASE NO.	SEX	AGE IN YEARS	DATE OF ADMISSION	DURATION OF SYMPTOMS BEFORE ADMISSION	ABDOMINAL PUNCTURE	OPERATION	TIME BETWEEN ONSET AND OPERATION	ORGANISM ISOLATED	DURATION OF DISEASE	COMPLICATIONS	OUTCOME
1.	F.	2	4/ 1/34	3 days	No	Yes	4 days	Type I Pneumococcus	6½ weeks	Abscess in L. I. Q.	Recovery
2.	F.	5½	12/21/33	20 hr.	Yes	No	—	Hemolytic streptococcus	15 weeks	1) Pneumonia 2) Empyema	Recovery
3.	F.	7	3/ 5/24	12 hr.	Yes	No	—	Pneumococcus	5 days	—	Death
4.	F.	6	5/27/24	12 hr.	No	Yes	15 hr.	Pneumococcus	14 weeks	Metastatic abscesses	Recovery
5.	F.	8	5/ 1/25	12 hr.	No	Yes	15 hr.	Culture sterile streptococcus	4 days	—	Death
6.	F.	9	8/23/26	36 hr.	No	Yes	39 hr.	Type II Pneumococcus	4 days	Meningitis	Death
7.	F.	6	2/ 8/28	24 hr.	No	Yes	26 hr.	Type I Pneumococcus	4 days	Terminal pneumonia	Death
8.	F.	6	8/ 2/28	2 days	No	Yes	2 days	Pneumococcus	7 days	—	Death
9.	F.	2	3/13/30	5 days	No	Yes	5 days	Type IV Pneumococcus	14 days	—	Death
10.	F.	10	3/23/29	4 days	Yes	Yes	6 days	Hemolytic streptococcus	7½ days	—	Death
11.	F.	6	9/10/31	2½ days	No	Yes	3½ days	Streptococcus	9½ days	—	Death

appendix was removed, and the abdomen was closed without drains. The culture of the abdominal fluid revealed Type I pneumococcus. The vaginal smear was negative for the pneumococcus. The pathologic report revealed an acute periappendicitis. Twelve days following operation the temperature rose to 102° F. and persisted for

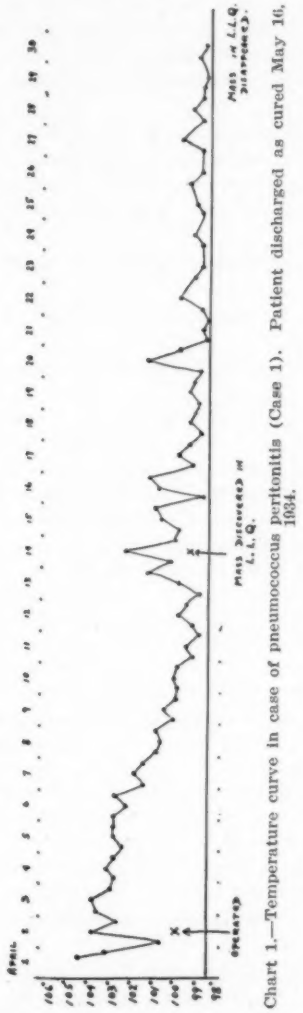

Chart 1.—Temperature curve in case of pneumococcus peritonitis (Case 1). Patient discharged as cured May 16, 1934.

about one week. At this time a mass the size of a hen's egg was found in the left lower quadrant above Poupart's ligament. Coincident with the fall of the temperature, the mass disappeared. The child was discharged six and one-half weeks after admission, entirely cured and weighing three pounds more than on admission (Chart 1).

CASE 2.—M. B., a five-and-one-half-year-old female child, was admitted on Dec. 21, 1933, because of severe, cramplike abdominal pains of twenty hours' duration. The child had always been well until five days before admission, when she developed a temperature of 105° F. This was ascribed to a throat infection. Coincidentally, a vaginal discharge which was found was treated with argyrol. The temperature came down to normal the following day, and the child was allowed up on the third day. Two days before admission, the temperature again rose to 104° F. Later, or twenty hours before admission, the child complained of severe cramplike abdominal pains, had about twelve watery stools and became listless. The past history was irrelevant.

Physical examination revealed a toxic, acutely ill child. The abdomen was slightly distended and tender. No definite rigidity was present, but there was a sense of resistence in both lower quadrants. The urethral meatus and vaginal introitus were found to be congested and inflamed. The remainder of the examination was entirely negative.

A diagnosis of acute generalized peritonitis was made—primary, or secondary to a ruptured appendix.

An x-ray examination of chest made on the day of admission failed to reveal any areas of consolidation.

The white blood count was 29,600, of which 88 per cent were polymorphonuclear leucocytes.

A peritoneal puncture was advised because the severe prostration of the patient contraindicated any other surgical procedure. About 0.5 c.c. of a turbid fluid was removed, which on culture revealed a hemolytic streptococcus. Culture of the vagina showed *B. coli* and *B. enterococcus*. Culture of the feces revealed *B. coli* and *B. enterococcus*. (No hemolytic streptococcus was found.)

With repeated transfusions, infusions, clyses, and cardiac stimulants, the child improved. The abdomen remained distended but became less tender. During the first ten days the child had marked diarrhea. Twelve days after admission the temperature rose suddenly to 106° F. Examination revealed dullness, bronchial breathing, and râles at the left base. The following day signs of an effusion developed. X-ray examination revealed a massive effusion. Twenty-three ounces of yellowish purulent fluid was removed. Culture of this fluid revealed the hemolytic streptococcus.

The chest was aspirated several times, and in two weeks the temperature began to reach normal. The abdominal tenderness persisted, especially in the right lower quadrant. The child then began to run a septic temperature, and because of the increased amount of pus in the chest a thoracotomy was performed on Jan. 29, 1934. Following this operation, the child ran a septic temperature for a long time. Repeated blood cultures were negative.

Three and one-half months after admission, the temperature came down to normal. The abdominal examination was negative. The empyema healed, and the child was allowed up. The patient was discharged as cured on Apr. 3, 1934, fifteen weeks after admission (Chart 2).

CASE 3.—M. S., a seven-year-old female, was admitted on Mar. 5, 1924, with pain and tenderness of twelve hours' duration throughout the abdomen. The onset was abrupt; the patient vomited several times; and the temperature rose to 102° F.

Physical examination revealed an acutely ill child. There was harsh breathing over the left chest but no râles. The abdomen was rigid, tender all over, but markedly so in the right lower quadrant. The umbilicus was protruding. The remainder of the physical examination was negative. The white blood count was 40,000, of which 90 per cent were polymorphonuclears.

A clinical diagnosis of lobar pneumonia with abdominal signs was made.

The day following admission x-ray examination of the chest failed to reveal any consolidation. An abdominal puncture produced a small amount of yellowish pus, which on smear revealed a gram-positive, lancet-shaped diplococcus.

The child was treated conservatively but expired five days after admission.

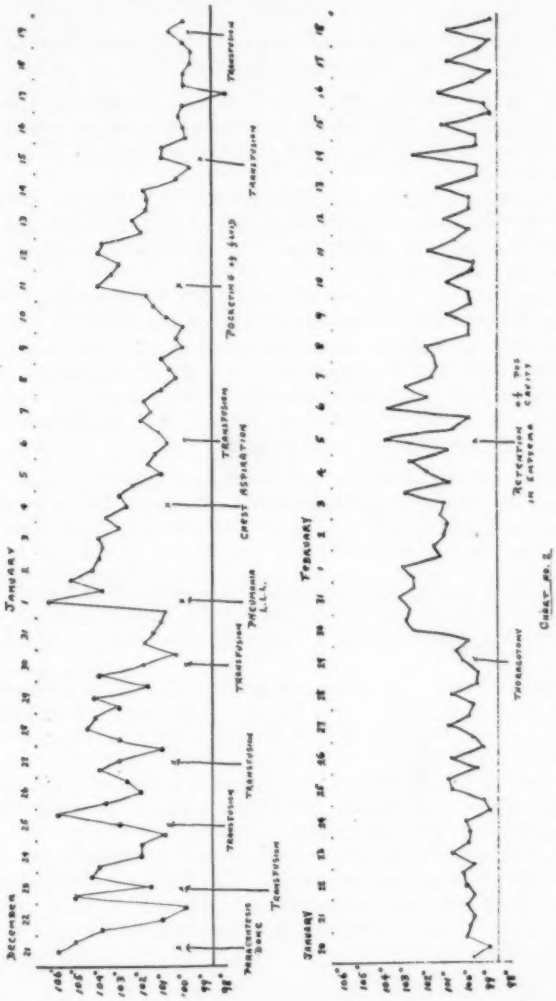

Chart 2.—Temperature curve in case of streptococcus peritonitis. Patient discharged as cured April 3, 1934.

CASE 4.—A. R., a six-year-old female child, was admitted on May 27, 1924, with a complaint of severe abdominal pain coming on suddenly twelve hours before admission. There was no diarrhea present.

Physical Examination: The temperature was 102.8° F. There was a distended, rigid, and tender abdomen. The remainder of the examination was negative. The white blood count was 29,850, of which 91 per cent were polymorphonuclear leucocytes.

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A diagnosis of acute generalized peritonitis was made—primary, or secondary to a ruptured appendix.

An x-ray examination of chest made on the day of admission failed to reveal any areas of consolidation.

The white blood count was 29,600, of which 88 per cent were polymorphonuclear leucocytes.

A peritoneal puncture was advised because the severe prostration of the patient contraindicated any other surgical procedure. About 0.5 c.c. of a turbid fluid was removed, which on culture revealed a hemolytic streptococcus. Culture of the vagina showed *B. coli* and *B. enterococcus*. Culture of the feces revealed *B. coli* and *B. enterococcus*. (No hemolytic streptococcus was found.)

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Three and one-half months after admission, the temperature came down to normal. The abdominal examination was negative. The empyema healed, and the child was allowed up. The patient was discharged as cured on Apr. 3, 1934, fifteen weeks after admission (Chart 2).

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Physical examination revealed an acutely ill child. There was harsh breathing over the left chest but no râles. The abdomen was rigid, tender all over, but markedly so in the right lower quadrant. The umbilicus was protruding. The remainder of the physical examination was negative. The white blood count was 40,000, of which 90 per cent were polymorphonuclears.

A clinical diagnosis of lobar pneumonia with abdominal signs was made.

The day following admission x-ray examination of the chest failed to reveal any consolidation. An abdominal puncture produced a small amount of yellowish pus, which on smear revealed a gram-positive, lancet-shaped diplococcus.

The child was treated conservatively but expired five days after admission.

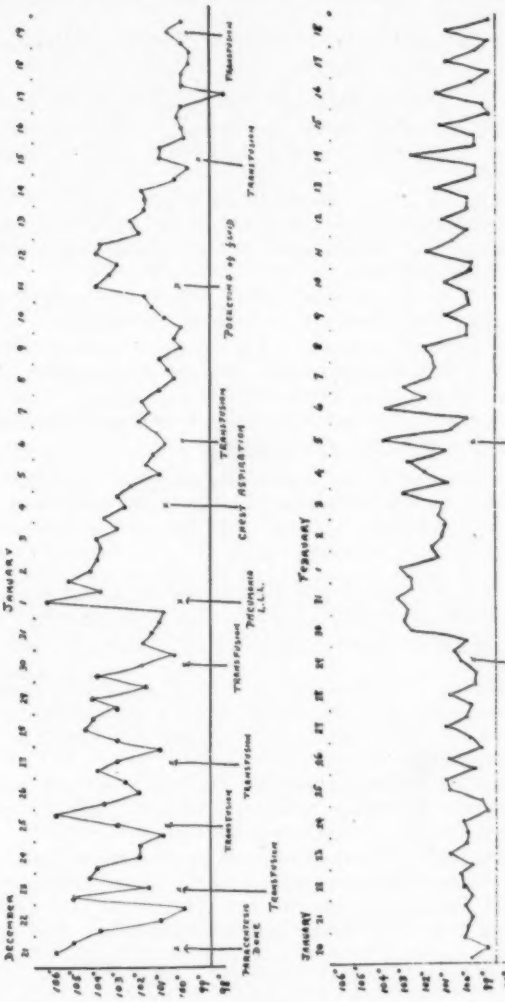

Chart 2.—Temperature curve in case of streptococcus peritonitis. Patient discharged as cured April 3, 1934.

CASE 4.—A. R., a six-year-old female child, was admitted on May 27, 1924, with a complaint of severe abdominal pain coming on suddenly twelve hours before admission. There was no diarrhea present.

Physical Examination: The temperature was 102.8° F. There was a distended, rigid, and tender abdomen. The remainder of the examination was negative. The white blood count was 29,850, of which 91 per cent were polymorphonuclear leucocytes.

A clinical diagnosis of acute appendicitis with peritonitis was made.

Operation was performed fifteen hours after the onset of the illness. On opening the peritoneum, a cream-colored, odorless pus was found. The ileum was distended and inflamed. The right tube was congested. An appendectomy was performed.

Smears of the pus revealed gram-positive, lancet-shaped diplococci. The pathologic report was acute periappendicitis. A blood culture taken five days later was positive for pneumococcus.

The patient was discharged as cured on Aug. 4, 1924, fourteen weeks after admission.

CASE 5.—C. S., an eight-year-old female child, was admitted on May 1, 1925, complaining of severe abdominal cramps and vomiting of twelve hours' duration. There was a history of an upper respiratory infection four days before the onset of the abdominal pain.

Physical examination revealed an undernourished acutely ill child. The temperature was 104° F. Herpes were present on the left cheek. There was slight dullness with suggestive breath sounds at left base. The abdomen was rigid, with marked tenderness in both lower quadrants.

A clinical diagnosis of lobar pneumonia with peritonitis was made, but an x-ray examination of the chest failed to reveal any areas of consolidation.

Operation was performed three hours after admission. A small amount of turbid fluid was encountered. The ileo-appendiceal region showed congestion. An appendectomy was performed, and the abdomen closed without drains. A culture of the peritoneal fluid was sterile. The pathologic report showed periappendicitis.

The patient died four days after admission.

NOTE.—The abdominal signs were preceded by an upper respiratory infection. In view of the negative peritoneal culture, this case cannot be definitely classified as pneumococcal or streptococcal in origin. The history, however, points to the latter.

CASE 6.—D. B., a nine-year-old female child, was admitted on Aug. 23, 1926, because of vomiting of twenty-six hours' duration. The onset was abrupt, awakening the child from sleep. Diarrhea and a high fever developed. No abdominal pain was present.

Physical Examination: The temperature was 103.6° F. The abdomen was distended, rigid and markedly tender. The vaginal introitus was injected, and a mucous discharge was present. The white blood count was 22,800, of which 92 per cent were polymorphonuclear leucocytes.

A clinical diagnosis of generalized peritonitis was made, and operation was performed three hours after admission. A markedly inflamed peritoneum with cloudy serous fluid was found. The pelvic cavity was drained.

The culture of the peritoneal fluid revealed a Type II pneumococcus. The following day the child developed meningeal signs. Lumbar tap revealed a cloudy fluid from which Type II pneumococcus was cultured.

The child expired Aug. 25, 1926, two days after admission.

NOTE: We feel that in this case the meningitis was secondary to a septicemia, having its origin in the primary lesion in the abdomen.

CASE 7.—E. R., a six-year-old female child, was admitted on Feb. 8, 1928, complaining of severe epigastric pain, vomiting, diarrhea, and fever of twenty-four hours' duration.

Physical Examination: The temperature was 104.6° F. The abdomen showed marked rigidity on the right side, with generalized tenderness. The remainder of the examination was negative.

A clinical diagnosis of generalized peritonitis was made, and operation was performed two hours after admission. A creamy colored pus was encountered. The appendix was removed, and the abdominal cavity was drained.

The culture of the abdominal pus revealed a Type I pneumococcus.

Two days later 50 c.c. of pneumococcus antibody solution was given.

The child died three days after admission. Necropsy revealed a terminal pneumonia.

CASE 8.—B. C., a six-year-old female child, was admitted on Aug. 2, 1928, complaining of abdominal pain of two days' duration. Diarrhea was not present.

Physical Examination: The temperature was 103° F. The abdomen was slightly distended, rigid in the lower half, and with marked tenderness throughout. The remainder of the examination was negative. The white blood count was 30,600, of which 88 per cent were polymorphonuclears.

Operation was performed one hour after admission to the hospital. A brown purulent fluid was encountered. The intestines were red and distended. The appendix was removed and the abdomen closed without drains.

Culture of the abdominal fluid showed pneumococcus.

The patient expired four and one-half days after admission.

CASE 9.—K. C., a two-year-old female child, was admitted on Mar. 13, 1930, with pain in the abdomen and fever of five days' duration. The onset was abrupt, awakening the child from sleep. For twenty-four hours before admission the child had persistent vomiting.

Physical Examination: The temperature was 103° F. The abdomen was distended and markedly tender throughout, especially marked in the right lower quadrant. The white blood count was 22,200, of which 82 per cent were polymorphonuclear leucocytes.

A clinical diagnosis of acute appendicitis with peritonitis was made. Operation was performed six hours later. Loops of small intestine were found to be inflamed, covered with fibrin, and adherent. The process was especially marked in the pelvis. A small amount of turbid fluid was present. The appendix was removed and the abdominal cavity was drained. Culture of the peritoneal fluid grew Type IV pneumococcus.

Whole blood was given intramuscularly.

The patient died nine days after admission.

CASE 10.—D. R., a ten-year-old female child, was admitted on Mar. 23, 1929, with a history of a "cold" of two weeks' duration with slight fever. Four days before admission the patient began to vomit, and the abdomen became distended. Two days before admission she began to complain of abdominal pain.

Physical Examination: The temperature was 103.4° F. The pharynx was congested. The abdomen was distended, tender, and rigid. The white blood count was 14,000, of which 90 per cent were polymorphonuclear leucocytes.

A clinical diagnosis of generalized peritonitis was made. An abdominal puncture revealed a clear fluid. Smear and culture of this fluid were negative. An x-ray examination of the chest failed to reveal any areas of consolidation. A blood culture was sterile.

Operation was performed two days after admission. A small amount of fluid was encountered, and the abdominal cavity was drained. A culture of the abdominal fluid revealed a short-chain hemolytic streptococcus.

The patient expired three and one-half days after admission.

CASE 11.—H. R., a six-year-old female child, was admitted on Sept. 10, 1931, complaining of abdominal pain of two and one-half days' duration.

Physical Examination: The abdomen was rigid and tender throughout. The remainder of the examination was negative. The white blood count was 24,800, of which 85 per cent were polymorphonuclear leucocytes.

A clinical diagnosis of generalized peritonitis was made.

Operation was performed twenty-four hours later. A sticky purulent exudate was encountered with fibrinous adhesions in the pelvic cavity. The viscera were congested, and the peritoneum had lost its luster. The abdominal cavity was drained.

A culture of the abdominal exudate showed a short-chain streptococcus. Despite transfusions, the child died one week after admission.

COMMENT

It is our opinion that the facts do not warrant acceptance of any single one of the theories thus far advanced as to the probable portal of entry of the organisms in primary pneumococcus or streptococcus peritonitis. The clinical pathologic picture strongly suggests that the organisms enter the abdominal cavity at the ileocecal-appendiceal region. It is impossible to prove whether the organisms reach this site through the genital tract, through the intestinal tract, through the lymphatic system, or by means of the vascular system.

Abdominal puncture should be performed more often in order to establish an early diagnosis. The objections against the use of this diagnostic measure may be classed as theoretical.

SUMMARY

1. Eleven cases of primary peritonitis occurring in children between the ages of two years and ten years of age are reported.

2. All of the cases occurred in females (seven pneumococcic and four streptococcic).

3. Abdominal puncture was performed in three cases.

4. Operation was performed in nine cases.

5. The general mortality was 75 per cent. Two patients with pneumococcus peritonitis were operated upon and recovered, and one patient with streptococcus peritonitis recovered without operation.

6. The questions as to the portal of entry and as to the most favorable time for operation still remain unanswered.

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26 EAST SIXTY-THIRD STREET

A SIMPLE METHOD OF TRANSFUSION FOR INFANTS AND CHILDREN

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CHICAGO, ILL.

BLOOD transfusions in the adult are relatively simple procedures. In the child they are more formidable. In the infant they are difficult and often unsuccessful. The greatest and practically the only difficulty is that of inserting a needle or cannula into a vein and keeping it there.

The procedure of finding a suitable vein and then threading it with a sharp needle can be used quite frequently. False moves of the operator or jerking of the patient frequently disrupt the transfusion by forcing the needle through the vein wall, a common accident. Unruly children and small or invisible veins add to the difficulty.

I should like to describe another method in which the vein is exposed and threaded with a blunt needle. The procedure is precise and should be attended with only a few failures. The various steps are not entirely original. They have gradually evolved as various groups of internes and residents have tried and changed the system.

Any vein may be used. We prefer the saphena magna which runs just anterior to the internal malleolus and then proximally along the inner aspect of the leg. The patient is placed on a suitable table with the operator at the foot facing the patient. The extremity is then fixed to a splint. This is extremely important for failure to do this will result in annoying motion at a later time.

The immobilizing is done by binding the foot to a padded splint as follows: a board, somewhat wider than the leg, which will reach from just above the knee to 1 or 2 cm. below the heel is wadded as a splint. It is applied to the lateral aspect of the leg. In this manner the foot will be externally rotated when the splint is flat on the table. With one-inch adhesive tape, the foot is bound to the board. From well on the underside of the board, the tape is rolled over the heel, along the inner aspect of the foot, then to the toes. This brings one to the other side of the splint. The tape then goes around the back of the splint arriving at the starting point. From here, it goes over the instep and then around the back of the board (Fig. 1).

A second light and not constricting band is placed around the knee, binding it to the board. The fixation of the foot is definite and positive

From the Children's Memorial Hospital, service of Dr. Joseph Brennemann.

if correctly done. If the binding is incorrectly executed, the child will be able to move his foot. This is more than annoying; it frequently means failure.

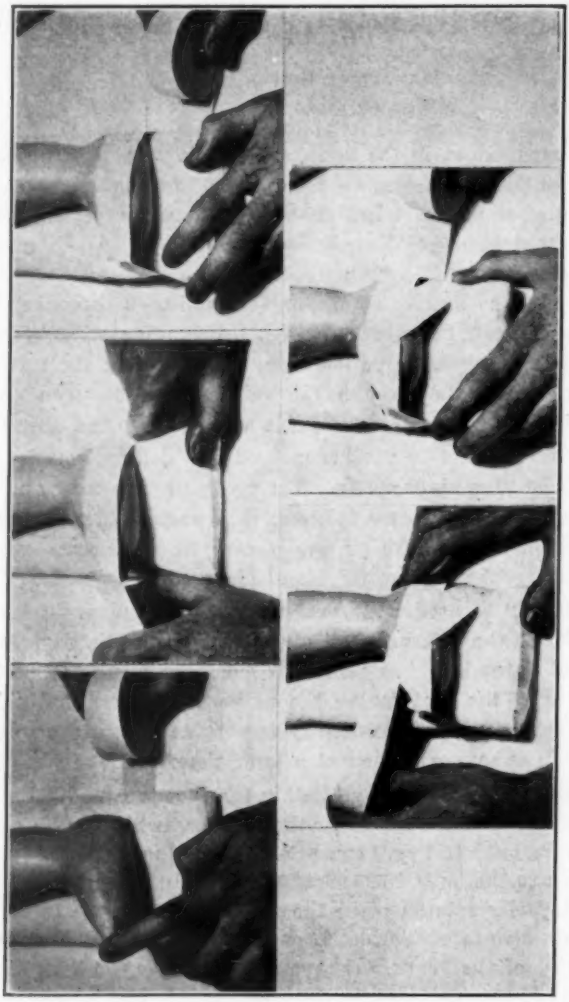

Fig. 1.—Binding the foot to the splint. The adhesive tape starts at the underside of the splint at the heel side, goes over the inner aspect of the foot, around the splint to the starting point, then over the instep, and around the splint again.

The next step is the locating of the vein to be used. If the vein is not visible, it may be brought out by distending it with a lightly applied tourniquet. We have found another method very useful. If one slides the finger firmly across the area where the vein is sought, one can feel the collapsed vein snap and roll back from the finger (Fig. 2*a*).

A second important step after identification of the vein, is that of marking it off on the skin. This marking must be one that will not disappear. This is accomplished after preparing the skin with iodine and alcohol as follows:

A 2 c.c. syringe is filled with 1 per cent novocaine and fitted with a gauge No. 25 or No. 26 needle. The novocaine is injected directly over the center of the vein. If the vein cannot be seen, one injects directly into the spot where the vein was felt. The wheal, of course, will blot out the actual sight of the vein, while the needle prick marks out the exact location of the underlying vein (Fig. 2*b*).

Any method of draping may be used, but here again we have made use of a simple procedure which will fit any examining or treatment

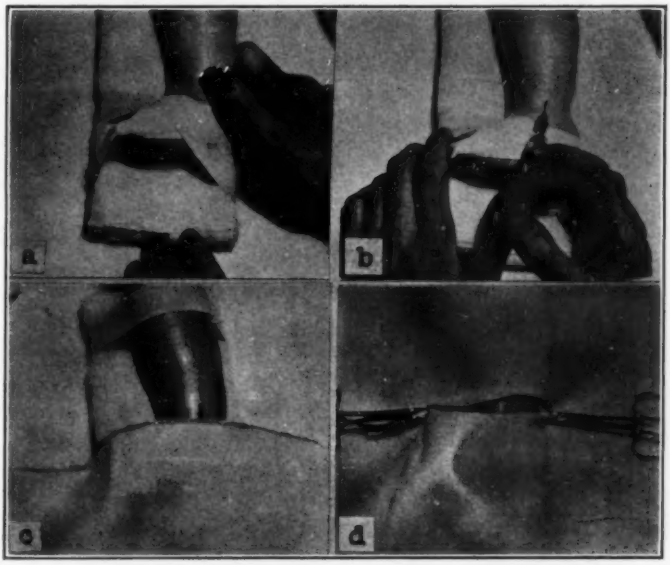

Fig. 2.—*a*, Palpating the vein; *b*, injecting the local anesthetic directly over the vein; *c* and *d*, the method of draping and placing the towel clips.

room. Three sterile towels are used and disposed as follows: one is placed on the table under the splint and leg; the second is placed across the leg with one edge just touching the needle mark; and the third parallels the second on the other side of the needle prick. It is essential that their edges meet.

Towel clips, one on either side of the foot, are used to fasten the towel edges to the splint. The field is then exposed by turning under the edges of the towels (Fig. 2*c* and 2*d*). This exposes a small field and, if done correctly, the needle mark will be in the center of it. One is now ready to incise and find the vein.

With a sharp-pointed knife, not a bellied one, a small incision is made at right angels to the vein, not parallel to it. The knife is held perpendicular to the skin; the incision is made with the point of the knife and not its edge. This is done by plunging the point of the

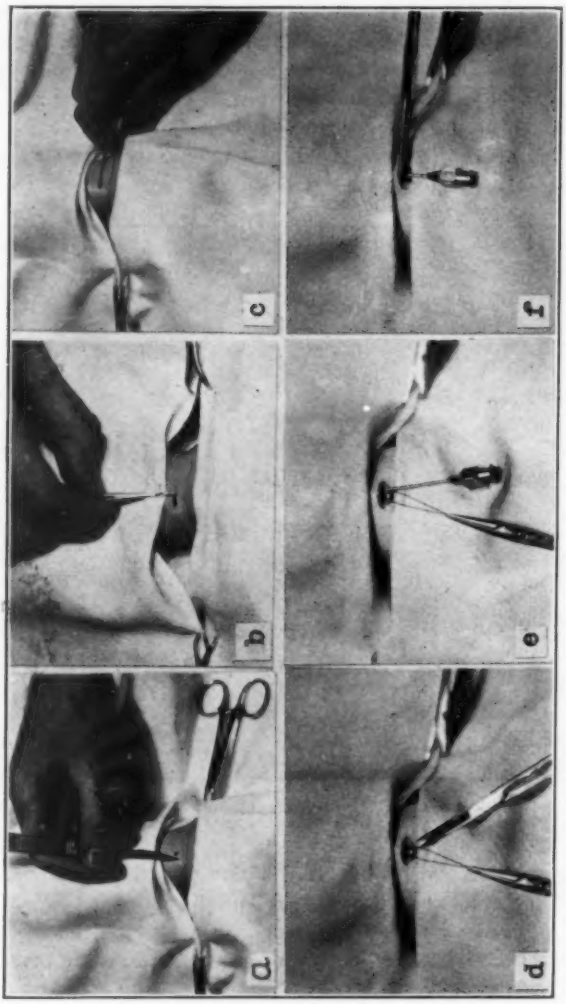

Fig. 3.—*a*, The method of holding the scalpel; *b* and *c*, the method of holding the forceps in finding and bringing the vein into view; *d*, the method of snipping the vein wall; *e*, inserting the needle; *f*, clamping the needle into place.

scalpel through the skin at a point 4 mm. to the left of the puncture wound of the local anesthesia and then drawing the knife to the right through the needle mark and continuing an additional 4 mm. By heeding these directions, the incision will be kept down to one of small size (Fig. 3*a*).

Frequently the incision will not have been made deep enough and the tough subcutaneous structures will refuse to reveal the subcutaneous fat in which the vein lies buried. This may be remedied with the point of the knife. The tissues are then spread apart and loosened by means of a mosquito forceps inserted perpendicular to the skin and spread in a direction parallel to the vein.

If the technic has been followed carefully, the vein lies directly under the center of the incision; it is not necessary, therefore, to see the vein in order to bring it to the surface. It is brought up by means of a thumb forceps with fine tangs. These tangs must not be too fine or they will pierce the vein, and yet they must not be too coarse or they will not pick up the vein. The instrument is held in the same manner that a surgeon holds a scalpel. It is pressed perpendicularly to the skin into the angle of the wound nearest the hand one works with, i.e., right or left. The forceps is pressed down until one meets with the resistance of the firmer tissues below. The hand is then de-

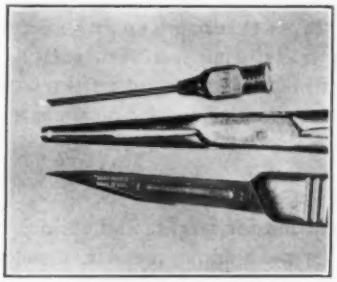

Fig. 4.—The blunt needle, the grooved forceps, and the sharp-pointed scalpel.

pressed, thus bringing the forceps to a horizontal plane. In this position one attempts to slide the forceps under the vein and to scoop it up by coming through to the other side of the incision and out. If this is successful, the vein will lie like a flat, glistening ribbon on the forceps (Figs. 3*b* and 3*c*).

A strand of No. 00 catgut is then grasped by the points of the forceps and pulled through. Its ends are brought together and caught with a small snap. This strand is used to put tension on the vein in order to facilitate the further steps. By means of a pair of small, sharp pointed manicure scissors, a nick is made in the wall of the vein on its upper surface (Fig. 3*d*). If the scissors is not sufficiently sharp or is sprung at the points, it will merely pinch the vein rather than cut it. A dot of red on the white vein indicates that the lumen has been opened; otherwise one may find that the adventitia alone has been incised.

The needle or cannula is now taken up and inserted into the prepared vein (Fig. 3*e*). The needle is of rustless steel, either gauge No.

20 or No. 18, depending upon the size of the vein. It is not a sharp needle, for such an instrument would readily penetrate the wall of the vein. This needle has had its point ground down to a 45 degree bevel. It is inserted into the vein with the bevel down. If it slides in easily, one is in the lumen; if not, one may be threading the adventitia. For very small veins—I refer to those of less than a millimeter in diameter—a hypodermic needle with its point removed may be used. Needles as small as gauge No. 26 may be used with success.

The needle is held in place by means of a mosquito forceps with a hole drilled through its tip as illustrated (Figs. 3*f* and 4). This is clamped on to the needle where it enters the vein. It serves to steady the needle and also to prevent leakage. If one has used a very small vein and has to resort to the hypodermic needle, a simple mosquito forceps undrilled will serve in a similar capacity.

To prove that one is in the vein, 5 or 10 c.c. of saline solution are injected. If all works easily, one has been successful.

This brings the operator to the point where most descriptions of transfusions begin. From this point on any apparatus or system may be used. When the transfusion has been completed, the vein is not tied off. Pressure will control bleeding until one can place a silk skin suture to close the wound. A firm dressing controls the oozing. The same vein can frequently be used again since it is not ligated.

SUMMARY

A method of transfusion for infants and children is described. Fixation of the part to be used, blunt needles, incision transverse to the vein, and locating the vein by feel rather than sight contribute to success.

NOTE:

Appended is a list of instruments and supplies put out in our "cutting down" set.

Padded splint
Roll of 1 inch adhesive tape

The following sterile materials put up in a sterile, deep covered tray ready for use:

3 Mosquito clamp forceps
1 Mosquito clamp forceps with needle groove in tip
1 Small needle holder for suturing
2 Sharp pointed tissue forceps without teeth
1 Bard-Parker knife with blade No. 11
1 Straight sharp-pointed manicure scissors
1 Suture scissors
2 Towel clamps
2 Curved skin needles
1 No. 24 hypodermic needle
1 Blunt No. 20 needle
1 Blunt No. 18 needle
2 Medicine glasses
1 2 c.c. syringe
1 10 c.c. syringe
1 Small vial No. 00 catgut
Sterile, fine skin silk
Sterile gauze
Sterile sponges

Other materials:

4 Sterile towels
1 per cent novocaine
Alcohol
Iodine

707 FULLERTON AVENUE

THE DETERMINATION OF THE INSENSIBLE WATER AS A MEANS OF CALCULATING THE HEAT PRODUCTION OVER A WEEKLY PERIOD

A Preliminary Report

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AN INDIVIDUAL, adult or child, loses weight imperceptibly and constantly through the excretion of water vapor from the skin and carbon dioxide by way of the respiratory passages. This occurs without any change in the body weight due to the ingestion of food or drink or elimination by the bowel or bladder. The physiologic loss of body weight in this manner is known as the "*perspiratio insensibilis*," "insensible perspiration," "intangible loss," "insensible loss" or "hourly loss."

The development of the concept of insensible loss began in 1614. Sanctorius considered the *perspiratio insensibilis* of such physiologic importance that for thirty years he weighed himself on a crude balance. His investigations were suggestive. The observations during the next 250 years were qualitative, therefore also mostly suggestive. Some of the observations dealt with the effect of various factors on the insensible loss as humidity, temperature, and seasonal loss.

Rubner in 1890 made significant quantitative additions by using a calorimeter in his experiments with animals. Later Atwater by the balance in connection with the respiratory calorimeter performed numerous accurate short experiments in adults. This was followed by Lombard of this medical school with meticulous balance observations on medical students. The work of Atwater and Lombard indicated that the loss of water vapor from the body might follow certain definite curves under standard conditions. In 1926 Benedict and Root reported the results of their observations on the hourly loss with the platform scales and a sensitive beam balance. Correlating their findings and the results of previous workers, they concluded that the rate of the hourly loss was proportional to the metabolism of an individual, that using the hourly loss in reference to the twenty-four-hour heat production, they could plot a straight-line curve indicating the metabolism, and that they could predict the twenty-four-hour heat production from the hourly loss.

From the Department of Pediatrics and Infectious Diseases, University of Michigan. Mead Johnson Infant Research Fund. Presented at the meeting of the University of Michigan Pediatric and Infectious Disease Society, November 24, 1934.

These and other observations indicated that under standard conditions of temperature, humidity, clothing, activity, and food the insensible loss expressed in terms of the percentage of heat lost by the vaporization of water from the body is fairly constant, being approximately 24 per cent of the total calories expended in a twenty-four-hour period.

Refinement of methods led to further study of the effect of changing environmental conditions on insensible loss; to the comparatively large daily variations when determined in short periods, to the greater accuracy of a twenty-four-hour determination or the weekly trend, to the effect of variation in the respiratory quotient, and to calculation of the insensible water from the metabolic mixture (Newburgh).

We may summarize the trend of the experimental progress in the determination and interpretation of the insensible loss of body weight:

1. *Perspiratio insensibilis* considered of great physiologic importance.
2. Qualitative measurement of this factor; experiments, suggestive.
3. Quantitative measurement of the hourly loss. Short experimental periods. Respiratory calorimeter used.
4. Measurement of the hourly loss by the balance and calorimeter simultaneously. Introduction of the exact effect of changing environmental conditions.
5. Acceptance of the sensitive balance as a less technical and more accurate method.
6. The relation of insensible loss to metabolism: their correlation and the prediction of the metabolism from the hourly loss.
7. Factors affecting the insensible loss: experiments determining the effect of temperature of the skin and the environment, humidity of the air, food, fasting, water intake, and sleep; age, sex, weight, and surface area; disease, such as hyperthyroidism, diabetes, eczema, epilepsy, obesity, malnutrition, diarrhea, and typhoid fever.
8. Consideration of the results obtained in short experimental periods compared with a twenty-four-hour period or the weekly trend.
9. Effect of the respiratory quotient on the insensible loss—variation may be from 82 to 104 per cent when the quotient is 1 to 0.707.
10. Calculation of the insensible water based on the metabolic mixture.
11. Effect of abnormal hydration of the tissues on the insensible loss.

Up to twenty years ago most of the observations on insensible loss were on adults. Since then there has been considerable work done with infants and children as subjects. Soderstrom and Du Bois, Bene-

diet and Hendry, Benedict, Meyer, Newburgh, Nobel and Rosenbluth, Sauer and McClure, McQuarrie, Levine, and others have reported observations on children. Some of the studies have been made using the calorimeter, others using the balance, and a few using the balance with the respiratory calorimeter as a check. Various phases of the problem have been approached: the effect of temperature, humidity, clothing, food, exercise, and body size—the effect of obesity, diabetes, marasmus, diarrhea, and eczema. Nearly all of these observations were done in short periods.

The above observations and the important conclusions to be drawn from them may be summarized largely from the recent work of Levine. Under standard conditions of temperature 22° to 26° C., of relative humidity 25 to 60 per cent and of basal conditions, the percentage of calories lost through the vaporization of water from the body was found to be approximately 24 per cent in normal children, 27 per cent in normal infants under one year of age, and 26 per cent in marantic infants. The relationship between the percentile dissipation of heat through the water vapor was shown in a general way to be applicable to infants, children, and adults.

By the balance method it has been shown that, as in adults, the loss in children is greater after food and exercise, less during sleep, and is moderately affected by the fluid intake, little affected by the usual range of humidity or by temperature, and not by clothes unless the clothes are so heavy that they induce sweating.

A correlation between the basal metabolic standards and the standards for insensible loss determined by the balance shows that the loss taken under basal conditions is probably dependable in predicting the metabolism in infants. It is probably applicable to other than basal conditions and to children as well as infants in the absence of visible perspiration. From experimental data normal basal standards of insensible loss have been proposed for normal and dehydrated infants referable to age, weight, height, and surface area. In pathologic conditions in children the percentile loss of heat through the evaporation of water is also approximately 24 per cent of the total heat production, though minor variations have been found to occur in eczema, diarrhea, marasmus, and myxedema. These observations point to the conclusion that the insensible loss, although proportional to age, height, weight, and surface area, although greater after the ingestion of food and after exercise, and although affected by sleep, temperature, and by disease (whether the subject is in the basal condition or is influenced by one of the above conditions) predicts the metabolism at that time fairly accurately (Table I).

Because technical difficulties incident to basal metabolic determinations in infants and children are great and estimations by balance

TABLE I

SUMMARY TABLE OF SOME INFANTS AND CHILDREN ON WHOM WATER VAPORIZATION HAS BEEN DETERMINED

SUBJECTS	DISEASE	OBSERVER	AGE	EXPERIMENTS	% OF CAL. LOST BY VAPORIZATION
8	Normal	Soderstrom and Du Bois	12-13	8	27.0*
1	Diabetic	Newburgh	9 yr.	1	24.6†
1	Nephritic	Newburgh	10 yr.	1	24.0†
1	Nephritic	Newburgh	16 yr.	1	28.0†
4	Normal	Levine	1-11 mo.	22	26.5*
7	Marasmus	Levine	1-11 mo.	30	25.6*
4	Normal	Levine	6½-10 yr.	28	24.0*
1	Obese	Levine	7 yr.	4	24.0*
1	Enlarged thyroid (symptom free)	Levine	10½ yr.	3	24.0*
1	Epilepsy	Levine	6½ yr.	3	20.0*
1	Cyclic vomiting	Levine	6½ yr.	6	26.0*
1	Acute lymphatic leucemia	Levine	11 yr.	1	20.0*
1	Subacute H. nephritis	Author	11 yr.	1	24.3‡

*Respiration calorimeter.
†Balance.
‡Seven-day period.

much less so, this procedure, as a measure of the metabolic rate, seems to offer clinical possibilities. It may also serve as a basic procedure in the study of water metabolism and the calculation of the total heat production.

Most of the observations in children have been done in short periods of time under basal conditions. Newburgh has shown in adults that the loss determined in a twenty-four-hour or longer period is more accurate, the loss being consistently close to 24 per cent of the total heat production. Therefore, he proposed a method in 1931 for the determination of the heat production over long periods of time under conditions of moderate activity. In all the subjects the diet closely approximated the energy transformation as shown by the trend of the weight. An insignificant amount of energy was transformed to mechanical work, and the subjects did not become uncomfortably warm or cool.

Under these conditions the average heat production is known and from the determination of the insensible water, the proportion of heat lost in this manner may be calculated and the result checked.

As a preliminary study of the application of this method to children, an eleven-year-old boy with symptom-free subacute hemorrhagic nephritis was confined to bed and the insensible loss determined daily for a period of seven days. His clothing consisted of a long, medium weight nightgown, the bed covering of a sheet, a light weight blanket, and a bedspread. The temperature of the room was approximately 70° F., the humidity, 45 per cent, and there was no visible perspiration throughout the observations. The rectal temperature changed less than 0.6° F. A sponge bath was given each day for comfort.

The weight of the subject was 21 kg. Eighty-five calories of food per kilogram, which I thought would meet his energy requirements, were allowed. The diet had the following composition: protein, 60.6 gm.; fat, 41.2 gm.; carbohydrate, 314 gm.; totaling 1,867 calories. Foodstuffs were used, the composition of which was known to be relatively constant or of which an analysis had been made. The weighed diet and the weight of the food eaten at each meal were obtained according to common practice. The subject's daily weight was obtained at 7:45 A.M. on a beam balance capable of weighing quickly to 1 gm. To obtain the weight of the water drunk, we used a large Erlenmeyer flask corked and fitted with a drinking tube. The flask was seated in crushed ice. The filled flask was weighed each morning, and the difference in weight between the filled and depleted flask gave the weight of the water drunk during a twenty-four-hour period. The excreta, urine and stools, were carefully collected each day and weighed on a balance accurate to 0.1 gram. The nitrogen excreted in the urine and stools was determined by the Kjeldahl method.

TABLE II

DETERMINATION OF THE INSENSIBLE LOSS IN WEIGHT BY THE BALANCE AND THE WEIGHT OF THE INGESTA AND THE EXCRETA IN A BOY WITH SUBACUTE HEMORRHAGIC NEPHRITIS

DAY ON DIET	WEIGHT (GM.)	WEIGHT OF H_2O (GM.)	WEIGHT OF FOOD (GM.)	WEIGHT 2 (GM.)	WEIGHT OF URINE (GM.)	WEIGHT OF STOOL (GM.)	A WT. 1 + WT. H_2O + WT. FOOD (GM.)	B WT. 2 + WT. URINE + WT. STOOL (GM.)	A – B INS. LOSS WT. (GM.)
4	21822	2219	1644	21767	2647	262	25685	24676	1009
5	21767	1470	1658	22100	1502	208	24895	23910	985
6	22100	1765	1579	22104	2222	157	25444	24485	959
7	22104	1987	1646	22620	2179	159	25737	24967	779*
8	22620	1271	1649	22836	1713	195	25540	24744	796*
9	22836	774	1637	23087	1099	161	25247	24347	900
10	23087	1697	1604	23083	2059	170	26388	25312	1016

*Fairly quiet in bed.

With the figures obtained in this manner we can determine the insensible loss in weight in a twenty-four-hour period by the following formula: insensible weight loss = beginning weight + water weight + food weight – end weight + urine weight + stool weight. Expressed in terms of the material metabolized, we have: $H_2O + CO_2 - O_2$ = insensible loss of weight.

It is established that with a knowledge of the water vaporized from the body we may calculate the rate of heat loss, for with the body temperatures between 22° and 25° C., the removal of each gram of water requires 0.584 calorie. To obtain the insensible water we use the formula, insensible H_2O = insensible loss – $(CO_2 - O_2)$.

Certain constants may be used to calculate the weights of the CO_2 and O_2 from the diet or the metabolic mixture. The composition of the diet of our subject was an approximation to his metabolic needs. A short preliminary period of three days was hardly sufficient to determine whether the subject's transformation of energy was in balance with his diet. Intermittent additions and subtractions of water from the tissues prevents such determination. I think, therefore, that it is best to calculate the weights of the CO_2 and O_2 and the total transformation of energy from the metabolic mixture rather than directly from the diet, though a simultaneous water balance study showed that the gain in weight during the period of observation was due to a shift in water balance and that the subject was in close caloric balance.

Calculation of the Insensible Water and the Total Transformation of Energy From the Metabolic Mixture.—The method of calculation is as follows:

First twenty-four-hour observation.

1. Insensible loss of weight
   Determined by balance and weights of
   Ingesta and excreta = 1009 gm.
2. Water vaporized.
   Insensible loss of weight – dietary carbohydrates × 0.41
   $1009 - (341 \times 0.41) = 1009 - 129$ = 880 gm.
3. Heat production of subject
   Water vaporized × $0.58 \times \frac{100}{24} = 880 \times 0.58 \times \frac{100}{24}$ = 1885.5 cal.

   1 – 2 – 3 = First approximation of the transformation of energy, or heat production.

4. Metabolic mixture =
   Protein = excreted nitrogen × 6.25 = 4.75 × 6.25 = 29.7 gm.

   = Protein oxidized, or 118.7 cal.

   Carbohydrate = = 314 gm.
   Fat = Total calories by first approximation –
   (calories from protein + carbohydrate) divided by 9.54
   $\frac{1885.5 - (118.72 + 1256)}{9.54}$ = 53.5 gm.

5. Composition of metabolic mixture × the constants to obtain $CO_2 - O_2$ output =
F. = 53.5 × (−0.08) = −4.3
C. = 314 × (0.41) = 129
P. = 29.7 × (0.08) = 2.4
127.1 gm. CO_2

6. Insensible H_2O = Insensible loss − $(CO_2 - O_2)$ =
1009 − 127.1 = 881.9 = 882 gm.

7. Heat production. Second approximation.
$$\frac{\text{Insensible } H_2O \times 0.58}{0.24} = 2131.2 \text{ cal.}$$

4 − 5 − 6 − 7 = Second approximation of the total transformation of energy.

8. The number of calories lost through the vaporization of water divided by the total transformation of energy in calories in twenty-four hours equals the percentile loss of heat over the total calories = $\frac{882}{2132.2}$ = 24 per cent

The total heat production and the insensible water were calculated for each twenty-four-hour period (Table III). The average insensible water for the seven-day period was 804.3 grams; the total heat production, 1917.1 calories; 804.3 × 0.58 = 466.49 = calories given off by vaporization; $\frac{466.49}{1917.1}$ = 24.3 per cent = the percentage of total heat removed by vaporization for the seven-day period, or weekly trend.

The average daily insensible water calculated from the diet = 785.8 gm. Diet, 1,867 calories = calories transformed, close approximation.

785.8 × 0.584 = 457.8 calories given off by vaporization.

$\frac{457.8}{1867}$ = 24.5 per cent total heat removed.

Table III

The Insensible Loss of Water and Its Percentile Relation to the Total Heat Production

DAY ON DIET	INSENSIBLE H_2O	INSENSIBLE H_2O CAL.	TOTAL HEAT PRODUCTION CAL.	PERCENTILE RELATIONSHIP
4	882 grams	511.56	2131.2	24
5	860	498.80	2078.3	24
6	883.7	483.55	2014.7	24
7	650	377.00	1571.0	24
8	667	386.86	1612.0	23.9
9	796	446.02	1858.4	24
10	891.5	516.97	2154.0	24
Averages and weekly trend	804.3 × 0.58 =	466.49	1917.1	24.3

SUMMARY

In a preliminary observation a method of calculating the heat production has been used in an eleven-year-old boy confined to bed under natural conditions. The diet closely approximated the transformation of energy over the weekly period. The insensible water was deter-

mined daily, and the heat production was calculated. The ratio of the percentile loss of heat to the total heat production amounted to 24.3 per cent as calculated from the metabolic mixture and 24.5 per cent as calculated from the diet.

The method seems to offer an accurate way of calculating the heat production for children at rest in bed over a weekly period.

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A CASE OF HEPATONEPHROMEGALIA GLYCOGENICA—VON GIERKE'S GLYCOGEN STORAGE DISEASE

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EXCESSIVE storage of glycogen, apparently due to disturbed carbohydrate metabolism, has been reported by several authors. Von Gierke[1] in 1929 reported two cases in which autopsy studies by Schönheimer[2] showed large amounts of glycogen stored in the parenchymal cells of the liver and kidneys. Wagner and Priesel[3] have stated their belief that a case reported by Wagner and Parnas[4] in 1921 belongs to this group. Schall[5] reported three cases of glycogen storage disease. Other cases have been reported by Worster-Drought and Weber,[6] Unshelm,[7] Warner,[8] van Creveld,[9, 17] Smith and O'Flynn,[10] Bischoff,[11] Loeschke,[12] Solomon and Anderson,[13] Rauh and Zelson,[14] Anderson and Vickery,[15] and Holmes á Court and Bray.[16]

From the description and findings of reported cases, the following diagnostic criteria seem to be established: early occurrence of asymptomatic hepatomegaly, chronic and nonprogressive in character, with or without familial history; absence of splenomegaly with increased deposit of subcutaneous fat, especially of the trunk; enlarged head with prominent brow and small extremities in comparison with the size of the trunk. The laboratory findings almost uniformly show ketonuria. Hypoglycemia has been found in some cases. Failure of mobilization of glucose, as shown by blood sugar determinations after giving epinephrine, has been reported by Schall,[5] Warner,[8] Anderson and Vickery,[15] and van Creveld,[17] but has not occurred in all cases. Normal blood cell counts and normal coagulation and bleeding times have been reported. There have been insufficient studies and records, thus far, to determine the diagnostic value of other laboratory findings. Autopsy records and histologic reports have shown marked storage of glycogen or glycogen-like substance in the parenchymal cells of the liver, the kidneys, in skeletal muscle, and in the heart and brain.

Because of the comparative rarity of this disorder and because of the additional information revealed, the following case is reported:

R. B., female, aged three and one-half years, was brought for examination because of her large abdomen. She was born at full term; delivery was normal, birth weight, 8 pounds 7 ounces. Both parents were well; one brother, ten years old, was normal; one sister died when eleven months old from encephalitis complicating coincident measles and whooping cough. There was no history of hepatomegaly or

From the Department of Pediatrics, University of Minnesota.
Presented at a meeting of Region III, Academy of Pediatrics, October 5, 1934.

enlarged abdomen in any member of the family. The patient was breast fed for nine months. Orange juice and cod liver oil were added at two months; cereal was started at five months; vegetables, at seven months; and a general diet was established at one year. The bowel movements had always been regular and normal. The child sat alone at eight months, walked at fourteen months, talked well at two years, and had always seemed alert and intelligent. At nine months and at eighteen months, the patient had an acute upper respiratory infection with fever and convulsions. The only other illnesses were whooping cough at two years and measles at two and one-half years. She had never been jaundiced.

At about six months the mother thought the baby was fatter than normal and noticed the head and abdomen were disproportionately larger than the extremities.

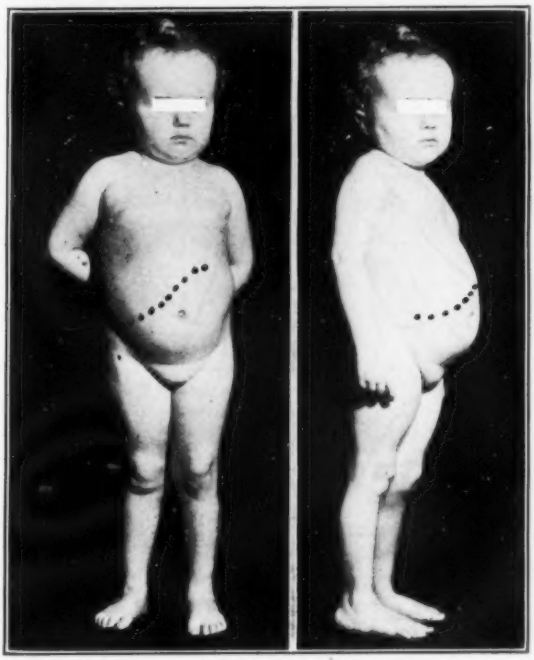

Fig. 1.—R. B., aged three and one-half years.

As she grew older, the child played normally but tired faster than her companions, would lie down at intervals for short periods of rest, and then resume her play. Recently climbing stairs caused her to complain of tiring, but there had been no other complaints.

Physical examination at three and one-half years showed a female child, cheerful and alert with a quick response to attention. She had a round, fat appearing head with a very short neck and a prominent brow. The abdomen protruded markedly. The trunk of the body was fat with a prominent pad of fat at the base of the neck posteriorly. A moderate amount of fine lanugo hair was present, distributed uniformly. In contrast to the body, the legs and arms were relatively thin and somewhat short. The legs showed a genu valgus. The scalp was clear; the hair, fine and moderate in amount. The skull circumference was 53 cm. The eyes, ears,

nose, and throat were normal. Twenty normal teeth were present. Glands and thyroid were normal. The abdomen was conspicuously large, 62 cm. in circumference at the umbilicus. This size was due partly to a thick deposit of subcutaneous fat and partly to a markedly enlarged liver. The liver extended from the fifth intercostal space in the right mammillary line to below the level of the right iliac crest (see Fig. 1). On the left, the lower border of the liver was felt 7 cm. below the costal border. A definite umbilical notch was palpable. The liver was smooth, somewhat soft, not tender. The spleen was not palpable. There was no evidence of ascites. Examination of the eyegrounds showed normal findings.

LABORATORY FINDINGS

Urine examinations were made on specimens obtained before breakfast, after the midday meal, and at night before supper, for a period of five days. Qualitative

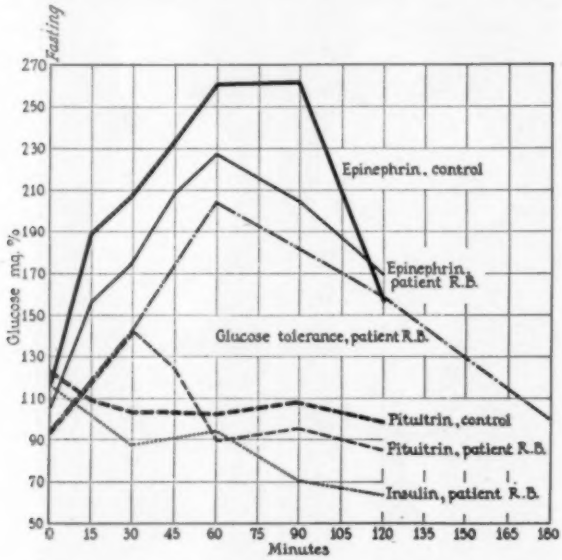

Fig. 2.—Blood sugar studies: glucose tolerance, 0.8 gm. per kilogram; epinephrine, 0.5 c.c. of a 1:1,000 solution injected subcutaneously in patient and a control; insulin, 5 units injected subcutaneously in patient; pituitrin, 0.3 c.c. injected subcutaneously in patient and a control.

tests for ketone bodies showed a daily output of acetone ranging from 0 to 4-plus. Diacetic acid in small amounts was present in two specimens. Other urine findings were normal. Diastase and amylase determinations were not made. The blood examination showed 78 per cent hemoglobin (Sahli); R.B.C., 4,150,000; W.B.C., 10,450; polymorphonuclear leucocytes, 43 per cent; lymphocytes, 57 per cent; eosinophile, 0; blood platelets, 210,000; bleeding time, 2 min.; coagulation time, 6 min.; icterus index, 8.5. Blood lipoid determinations showed no evident disturbance of fat metabolism. Total fatty acids were 504 mg. per cent; cholesterol, 186 mg. per cent; iodine number, 109.

Studies of blood sugar, including fasting blood sugar, the glucose tolerance test, epinephrine, insulin, and pituitrin tests showed no significant changes from normal (see Fig. 2). Fasting blood sugar readings ranged from 93 mg. per cent to 120

mg. per cent. Glucose, 0.8 gm. per kilogram of body weight, was given by mouth. A normal glucose tolerance curve was obtained. Glycosuria did not occur. Five units of insulin were given with a lowering of blood sugar to 65 mg. per cent. Epinephrine, 0.5 c.c. of a 1:1,000 solution, was given subcutaneously and a similar amount given to a normal child for control. Fig. 2 shows no marked abnormality of epinephrine response.

Pituitrin test: 0.3 c.c. anterior pituitary lobe extract was given subcutaneously on a fasting stomach. Blood sugar readings were made at fifteen-minute intervals the first hour and at thirty-minute intervals the second hour. A similar test was made on a normal control. The results showed no alteration in

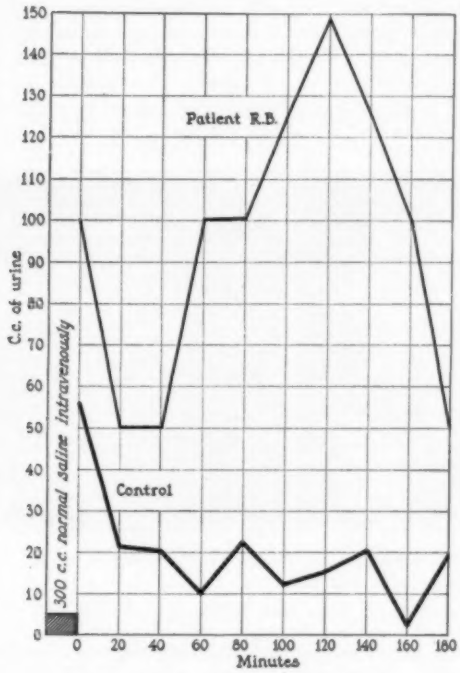

Fig. 3.—Liver water storage test.

the blood sugar level in the control. There was a slight initial rise of blood sugar in the patient followed by a return to normal and a continued normal level at the end of one hour (see Fig. 2).

Based on the work of Lamson and Roca[18] and Pick,[19] a test of liver water storage ability was made. These workers showed that in normal dogs excess water given intravenously was quickly withdrawn and stored in the liver, then slowly released, and eliminated as urine over a period of two to three hours. When the liver was withdrawn from the circulation by means of an Eck fistula or by ligation of the afferent vessels, storage of water in the liver did not occur. The excess fluid was eliminated in the urine in the space of about one hour. According to the postulation that the liver cells in this patient were full of glycogen, there would not be room for storage of water, and one should get a water elimination

curve similar to that in a dog with an Eck fistula. Three hundred cubic centimeters of normal saline solution were given intravenously to both the patient and a normal control. The response is shown in Fig. 3. Following the intravenous administration of 300 c.c. of normal saline to a normal child as control, the urine output at twenty-minute intervals dropped from 55 c.c. to an average output of about 15 c.c. throughout a period of three hours. A like amount of normal saline similarly given to the patient gave an output of urine increasing at twenty-minute intervals to 148 c.c. at the end of two hours with apparent termination of the diuresis at the end of three hours. This curve closely resembles that observed by Pick[19] on dogs with an Eck fistula.

The x-ray findings showed no involvement of the long bones. Examination of the abdomen, Fig. 4 *A*, showed a very large liver with evident enlargement of the right kidney. A lateral skull plate (Fig. 4 *B*) shows the sella turcica within normal limits, but depressed, along with the whole middle cranial fossa. The petrous portion of the temporal bone is also depressed. This is taken as suggesting the presence of internal hydrocephalus, probably more marked in the third ventricle.

A Mantoux, a Wassermann, and a van den Bergh test were negative.

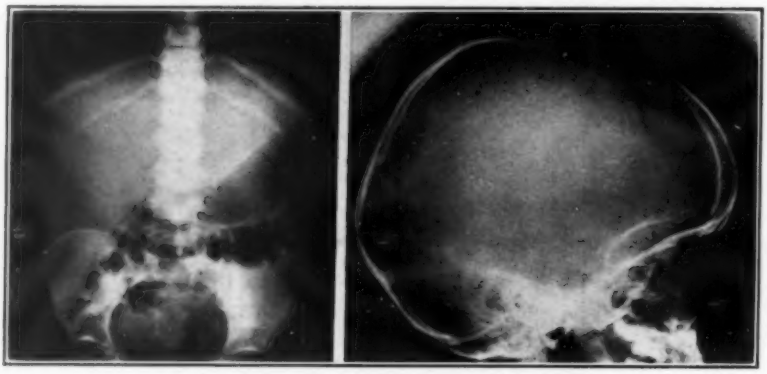

Fig. 4.—X-ray pictures of abdomen and of skull.

COMMENT

A diagnosis of hepatonephromegalia glycogenica as described by von Gierke[1] seems most probable. This opinion is based on the early onset of the enlarged abdomen (at six months), the absence of symptoms, and the physical appearance of the child with Olympic brow, large head and trunk, with relatively small limbs. Further, supporting this diagnosis, is the marked enlargement of the liver, the increased size of the x-ray shadow of the right kidney, the absence of enlargement of the spleen, the absence of ascites, the absence of history of jandice together with normal van den Bergh test, normal heart findings, the normal blood picture, and the decreased water storage ability of the liver. Finally, the presence of acetonuria which, although variable, in single specimens, was constant in its daily occurrence. Although epinephrine effect on the blood sugar level in this case was apparently

normal, contrary to the findings of Schall,[5] Warner,[8] Anderson and Vickery,[15] and van Creveld,[17] it seems possible that the underlying cause of disturbed carbohydrate metabolism may vary in different cases, so that the response to epinephrine might also vary. Thus Schönheimer[2] was able to demonstrate a lack of diastase in the liver, as the underlying factor in von Gierke's cases. Unshelm[7] favors the theory of abnormal attachment of glycogen to protein, while Rauh and Zelson[14] believe there may be alteration of cell permeability shown by increased diastase in the urine. The present case raises the question of whether a similar clinical picture of hepatomegaly might result from disturbed carbohydrate metabolism as the result of internal hydrocephalus with pressure changes in the region of the hypothalamus and pituitary gland. Although there are no histologic data in this case upon which the diagnosis of glycogen storage disease can be proved, I believe the evidence available justifies placing the case of this child in this group.

Further study on the pituitary relationship to glycogen storage disease seems to be indicated.

SUMMARY

1. A case of hepatonephromegaly in a three and one-half-year-old female child with the diagnosis of von Gierke's glycogen storage disease is reported.

2. Laboratory studies show ketonuria, impaired water storage ability of the liver, with x-ray evidence of internal hydrocephalus.

3. The suggestion is made that disturbed pituitary function may play a part in the etiology of glycogen storage disease in this case.

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ANEMIA OF THE NEWBORN AND ERYTHROBLASTOSIS—ARE THEY INSEPARABLE?

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SINCE Ecklin[1] described the first clearly recognized case of anemia of the newborn in 1919, reports of this disease have been seeping into the literature in ever increasing numbers. The first cases reported were distinguished hematologically by the presence of large numbers of erythroblasts in the circulating blood.[1, 2] In more recent years, this primary erythroblastic anemia of the newborn has been correlated with icterus gravis and universal edema of the newborn because they all have in common as a basic feature this erythroblastosis, encountered not only in the blood, but in organs.[3, 4, 5, 6, 7] In the bone marrow, but more particularly in the liver, spleen, kidney, and other viscera, there is a persistence of embryonal hematopoiesis.[5, 6, 7] The concurrent association of these three symptoms, anemia, severe icterus, and edema, in the newborn has been particularly emphasized by De Lange[3] and Baar and Stransky[4] abroad, by Blackfan and his coworkers[5] and by Arthur Abt[6] in this country.

Primary erythroblastic anemia of the newborn is characterized by a severe hyperchromic anemia with a high color index, a conspicuous number of macrocytes, and reticulocytosis. The anemia belongs in the hemolytic category, for there is increased bilirubin formation from the hemoglobin of the destroyed red blood cells with increased urobilin excretion in the urine and stool. This tremendous conversion of bilirubin from hemoglobin causes a marked jaundice. The excessive formation of bilirubin may result in bile thrombi and pathologic liver conditions, which in turn cause a hepatogenous or obstructive form of jaundice, so that the van den Bergh reaction is then a promptly direct positive or biphasic and bile is present in the urine.[5, 6] In addition to the large number of nucleated red blood cells and the hyperchromic anemia, the blood regularly exhibits leucocytosis with a shift to the left, frequently a thrombopenia and an increased bleeding time, although hemorrhagic phenomena in this disease are not conspicuous. General edema of the infant, as has been pointed out,[3-5] is an added feature in some cases. Pathologically, erythropoietic centers of the embryonal type persist in various organs and are prominent at postmortem histologic examination.[5, 6, 7] There is a deep yellow green staining (bile) of all the internal organs and serous membranes. The

From the Newborn Service of the Jewish Maternity Hospital and the Children's Division of Beth Israel Hospital, New York City.

bone marrow is either normal or shows moderate degree of erythropoiesis of both red and white cell series, with often a diminution of megakaryocytes. Almost invariably hemosiderosis, a sequel of red blood cell destruction, is found in the kidneys and the reticuloendothelial system.[3, 5, 6] This is a manifestation of iron storage and conservation, for iron is a precious metal to the body.

Is erythroblastosis the underlying and inseparable component of all cases of primary anemia of the newborn? The characteristic symptoms, laboratory findings, and pathologic features have been described here in some detail in order to contrast it with what I believe is a different variety of anemia of the newborn. The latter is different clinically, hematologically, and pathologically from the already accepted type of erythroblastic anemia. The blood picture in this second type of congenital anemia is also distinguished by a hyperchromic, macrocytic anemia, and leucocytosis with a shift to the left, but here the resemblance practically ceases. Erythroblasts are either not present at all or found in the small numbers normal for the newborn. Jaundice is not marked and may even be absent. The blood serum, if it reveals an increased bilirubin content, will yield only an indirect van den Bergh reaction, with slightly increased figures. Bile is not found in the urine. There does not seem to be any increase of urobilin formation. The leucocytic reaction is the same, but the number of blood platelets is normal, as is the bleeding time. The reticulocytes are usually either normal in number or but moderately increased—in striking contrast to the erythroblastic anemia of the newborn. Pathologically, there is no intense bile staining of the organs and serous membranes; no embryonal erythropoietic centers are found in the viscera; and hemosiderosis is not encountered.

This form of anemia, while it bears some resemblance to posthemorrhagic anemia, has neither clinical nor necropsy studies to support this belief. If the drop in the hemoglobin content is sudden, the consequent appearance of air hunger simulates a massive hemorrhage, but the acute shock which is part of the picture of massive hemorrhage is lacking.[8] At autopsy, true cases of congenital anemia of the newborn, whether with or without erythroblastosis, show no internal hemorrhage. Furthermore, the characteristic hyperchromic anemia is different from the anemia secondary to hemorrhage. This nonerythroblastic primary anemia of the newborn has been definitely recognized by Stransky[9] and Finklestein,[10] who call it the aregenerative type. Some early past cases fall into this category,[5,*, 11, 12, 13] but more recently Pasachoff and Wilson's[14] case, Pritchard and Smith's,[15] and most recently that recorded by Brown and his associates.[16] This last case, both from a clinical and laboratory standpoint, fulfills the criteria just

*Cases 4, 6, and 7 of Blackfan, Baty and Diamond's series.

enumerated for establishing the diagnosis of nonerythroblastic anemia of the newborn. Yet careful postmortem studies revealed not only no concealed hemorrhage, but detailed histologic sections demonstrated the absence of erythropoiesis in the viscera, a poverty of bone marrow erythropoiesis, no hemosiderosis, no change in pathologic conditions in the liver, spleen, or kidney.

A case illustrative of this type of anemia follows:

Baby G, female, was born 4:05 P.M., Sept. 5, 1934, at the Jewish Maternity Hospital. She was the third child; the other two were normal. The mother had been treated in the prenatal clinic regularly since January. Aside from the usual nausea and vomiting during the early part of pregnancy, she had felt very well. Her diet throughout the pregnancy was liberal and varied.

After seventeen hours and forty-five minutes of labor, spontaneous birth took place. It was noticed immediately that the amniotic fluid and the vernix caseosa were deeply colored orange. The baby was similarly stained as if she had been dipped in methyl orange. The placenta was noticed to be rather large but otherwise not grossly abnormal. Consequently it was not examined histologically, which omission may have been unfortunate, as the question of erythropoiesis solely in the placenta has been raised.[17, 18] On examination, besides the curiously orange color of the skin and nails, there was no abnormality except a firm spleen about 1 cm. below the costal arch. Because of the known association of orange amniotic fluid with anemia of the newborn, we were curious to see whether the latter would develop. The mucosa and sclera were normal in color, and there were no signs of jaundice. The urine and stools were normal in appearance. Unfortunately, no blood count was made immediately after birth.

The baby was permitted to nurse, but on failure to gain, complementary feeding was instituted. On September 12 the fact that the baby was growing pale became manifest. The baby was then six days old.

The blood count showed:

Hemoglobin, 32%
Red blood cells, 1,130,000
Color index, 1.4
White blood cells, 19,600

Differential count:		
	Segmented cells,	55%
	Staff cells,	6%
	Eosinophiles,	1%
	Myelocytes,	1%
	Metamyelocytes,	2%
	Lymphocytes,	31%
	Mononuclear cells,	4%

The blood smear showed only 1 normoblast per 100 white cells and a preponderance of macrocytes, as well as poikilocytosis and anisocytosis.

The child looked bad and nursed poorly; the spleen was still firm and enlarged; its turgor was poor; but it showed no air hunger or shock. A transfusion of 75 c.c. was given, and 30 c.c. of whole blood was injected intramuscularly. She began to look better. The spleen became smaller, and the hemoglobin content rose to 50 per cent.

On September 16, she began to vomit, pallor increased, the respirations became rapid, and oxygen was given for a few hours, but the child was not in the state of shock. The blood count then was:

Hemoglobin, 44%
Red blood cells, 1,720,000
Color index, 1.25
White blood cells, 20,000
Reticulocytes, 0.5%
Differential count:

Segmented cells,	52%
Staff cells,	5%
Eosinophiles,	1%
Myelocytes,	2%
Metamyelocytes,	1%
Lymphocytes,	33%
Mononuclear cells,	6%

Examination of the entire blood smear showed 3 normoblasts and 1 megaloblast. There was marked macrocytosis, polychromatophilia, basophilic stippling, and poikilocytosis. The stool examination showed no gross blood. A suspicious benzidine reaction, when repeated, was negative. Both stool and urine showed no urobilin, a fact which argued very much against a hemolytic process as the cause of anemia. The bile content of the stool was normal, and there was no bile in the urine. The child was never jaundiced at any time.

On September 17 another transfusion of 50 c.c. was given.

The child began to improve again, but the spleen was still palpable. On September 21 the blood count was:

Hemoglobin, 60%
Red blood cells, 2,610,000
Color index, 1.1
White blood cells, 9,500
Reticulocytes, 1%
Differential count:

Segmented cells,	38%
Staff cells,	2%
Eosinophiles,	3%
Myelocytes,	1%
Metamyelocytes,	2%
Lymphocytes,	44%
Mononuclears,	9%
Basophiles,	1%

The blood smear showed less marked macrocytosis as well as less marked polychromatophilia and poikilocytosis.

The child continued to look good and was taking her feedings well, gaining weight; on September 25 the blood count was:

Hemoglobin, 58%
Red blood cells, 2,700,000
Color index, 1.05
Platelets, 367,000
Reticulocytes, 1%
White blood cells, 9,400
Differential count:

Segmented cells,	35%
Staff cells,	2%
Eosinophiles,	1%
Basophiles,	1%
Myelocytes,	1%
Mononuclears,	8%
Lymphocytes,	52%

The blood smear was the same as in the last examination again with a conspicuous absence of nucleated red blood cells.

The child was sent home the next day, still somewhat anemic; the spleen was firm and easily felt; stools and urine were normal; the infant was eating well and gaining weight. Saccharated carbonate of iron, 10 grains three times daily, was prescribed.

The course of the child was followed, and, except for two attacks of diarrhea and vomiting, she improved steadily. She ate well and gained weight; however, when she was three months old, the spleen was still enlarged. The blood count was as follows on Nov. 28, 1934:

Hemoglobin, 76%
Red blood cells, 3,460,000
Color index, 1.1
White blood cells, 7,600
Platelets, 100,000
Reticulocytes, 1.5%
Differential count: Segmented cells, 28%
Eosinophiles, 2%
Mononuclears, 5%
Lymphocytes, 65%

The smear showed slight anisocytosis with a few macrocytes.

TABLE I

SUMMARY OF BLOOD EXAMINATIONS OF BABY G.

	6 DAYS OLD	↓ TRANSFUSION 10 DAYS OLD	↓ TRANSFUSION 15 DAYS OLD	19 DAYS OLD	12 WK. OLD
Hemoglobin	32%	44%	60%	58%	76%
Red blood cells	1,130,000	1,720,000	2,610,000	2,700,000	3,460,000
Platelets				367,000	100,000
Color index	1.4	1.25	1.1	1.05	1.1
White blood cells	19,600	20,000	9,500	9,400	7,600
Segmented cells	55%	52%	38%	35%	28%
Staff cells	6%	5%	2%	2%	
Eosinophiles	1%	1%	3%	1%	2%
Myelocytes	1%	2%	1%	1%	
Metamyelocytes	2%	1%	2%		
Lymphocytes	31%	33%	44%	52%	65%
Mononuclears	4%	6%	9%	8%	5%
Basophile			1%	1%	
Reticulocytes		0.5%	1%	1%	1.5%
Normoblasts	196 per c.mm.	120	0	0	0

This case, aside from illustrating the nonerythroblastic type of congenital anemia, brings out two important clinical points. A baby born with a skin colored orange because of deep yellow amniotic fluid and golden vernix caseosa is destined to develop anemia. This has been emphasized by several different observers[3, 5, 6, 9, 18] Such a baby should be watched critically every day. When the anemia develops, the child should be promptly and, if necessary, repeatedly transfused. It is my opinion that the transfusions in this case were life-saving. The indication for repeated transfusions is repeated drops in the hemoglobin.

The clinical picture in this case had none of the features of massive hemorrhage, of which the concealed suprarenal hemorrhage is a classic example.[8] Only once, just before the last transfusion, did the baby have what might be interpreted as air hunger, and she quickly recovered from this; she never suffered from shock. Aside from the color

of the skin, the enlarged spleen was the only clue to an abnormality of the blood. The leucocytosis is characteristic of the acute phase of the anemia, as is the presence of young white cells in the blood. The embryonal hematopoietic centers often show young cells of the myeloid series.[14-16] The return of the number and type of white cell to what is normal to a newborn, is contemporaneous with the improvement in red cells and hemoglobin content. This inverse ratio between the high white cell count and the low red cell count is a constant feature of all cases of congenital anemia. It is to be noted that the reticulocytes during the stage of acute anemia were 0.5 per cent but rose to 1.5 per cent as the hemoglobin content and number of red blood cells rose, as regeneration set in.

The time of onset of this anemia of the newborn varies from one hour to one day[11] or a week[21] or longer.[12] On the other hand Segar and Stoeffler,[20] who had three cases of anemia of the newborn in three successive siblings, discovered the anemia of the first baby when it was a few weeks old. The second baby had definite anemia at the end of the first week. The third baby had a normal hemoglobin content and red cell count until the seventh day, when the count fell precipitately, the hemoglobin content dropping from 78 per cent to 47 per cent, and the red cell count falling from 3,700,000 to 2,200,000. This sudden, terrific fall was characteristic of my case on two occasions and has been also the general experience of those who have reported such cases. I must emphasize again that there were no signs of hemorrhage, and postmortem studies also reveal no concealed hemorrhage. The fact that a baby one hour old had a marked anemia bespeaks an intrauterine origin. This is supported by studies which show erythroblastosis in the placenta.[17] On the other hand, in some cases in which the count was made daily, a normal count prevailed for the first week or two of life. The diet or health of the mother does not seem to account for the anemia of the baby though Clifford and Hertig[18] report a case in which the mother had a postpartum hemorrhage after each childbirth, but we have all seen repeated postpartum hemorrhages in women whose children did not have anemia. The relatively late onset of the anemia in some cases either excludes an intrauterine origin or else we must assume that the toxic factor has a variable and, at times, a long incubation period.

In the first case, we have witnessed anemia of the newborn without erythroblastosis. In the following case we meet erythroblastosis without anemia, but marked by such intense jaundice that congenital obliteration of the bile ducts was suspected before the blood studies were made. The course of the disease finally definitely excluded this diagnosis, for at the age of five months the baby was perfectly well.

Baby S, male, was born June 6, 1934, a full-term child; he was cyanotic at birth but was revived without difficulty. He was the third child; other two were normal.

On June 7 the baby was noticed to be extremely jaundiced; spleen and liver were not felt.

On June 8 the jaundice was still more marked. The baby appeared sick, nursed fairly well, losing only 4 ounces. Temperature was normal. The liver was not palpable, but the tip of the spleen was just felt. The urine was very dark, containing bile but no urobilin.

Blood count was as follows:

Hemoglobin, 92%
Red blood cells, 3,690,000
Color index, 1.2
Reticulocytes, 18.7%
White blood cells, 23,900
Normoblasts, 23,000 per c.mm.
Differential count:

Segmented cells,	55%
Staff cells,	8%
Eosinophiles,	3%
Basophiles,	1%
Myelocytes,	1%
Myeloblasts,	2%
Metamyelocytes,	1%
Mononuclears,	8%
Lymphocytes,	21%

The smear showed marked macrocytosis ,polychromatophilia, and poikilocytosis. Clot retraction time was forty-five minutes. The serum was deeply yellow.

On June 9 the jaundice was the same; liver, not enlarged; spleen, just palpable; no hemorrhage visible.

On June 10 infant was lethargic. The skin turgor was poor. He took his feedings poorly. Three hundred cubic centimeters of saline solution were given subcutaneously. A transfusion of 60 c.c. was also given.

On June 11 the jaundice was as marked as ever; the general condition continued to be poor.

The blood count was as follows:

Hemoglobin, 100%
Red blood cells, 4,000,000
Color index, 1.25
White blood cells, 20,000
Polymorphonuclears, 38%
Eosinophiles, 2%
Lymphocytes, 56%
Mononuclears, 4%

The smear revealed only two normoblasts per 100 white cells. Macrocytosis, polychromatophilia, and poikilocytosis were present as before.

On June 12 spleen was still enlarged; the liver was not. The stool was negative for bile and for blood. The blood count was:

Hemoglobin, 108%
Red blood cells, 4,000,000
Color index, 1.3
White blood cells, 15,400

Only two normoblasts per 100 white cells were seen on the smear. Another transfusion of 60 c.c. was given.

By June 15, for the first time, jaundice was less marked, and the condition was slightly improved since the transfusion. He had gained three ounces; the spleen had become larger, now being felt 1 inch below the costal margin.

On June 18 the general condition was worse again. The jaundice was more marked. Stool showed presence of bile but no urobilin. Although the hemoglobin was 100 per cent, the third transfusion of 60 c.c. was given.

On June 20 the general condition was improved; the jaundice was less marked. He was taking his food better.

On June 21 the blood count was:

Hemoglobin, 90%
Red blood cells, 4,300,000
Color index, 1.1
White blood cells, 18,950
Reticulocytes, 3.2%
Differential count:

Segmented cells,	34%
Staff cells,	8%
Myelocytes,	2%
Promyelocytes,	1%
Eosinophiles,	3%
Mononuclears,	7%
Lymphocytes,	45%

Smear showed anisocytosis and polychromatophilia, but little macrocytosis.

On June 23 the spleen was getting larger, and the stools were loose. He was still very jaundiced.

On June 26 a fourth transfusion of 66 c.c. was given.

On July 2 the icteric index was 110; van den Bergh reaction, promptly positive —25 units. The jaundice was extreme, and the infant was not gaining weight in spite of adequate calories.

On July 5 spleen was still 1 inch below the costal margin; the liver was enlarged and about 1.5 inches below the costal margin. The jaundice was still extreme; the stools clay colored again, the test showing absence of bile.

The blood count made on July 6 was as follows:

Hemoglobin, 88%
Red blood cells, 4,780,000
Bleeding time, 2.5 min.
Coagulation time, 3.5 min.

A fifth transfusion of 60 c.c. was given.

After this the baby steadily improved, the jaundice gradually decreasing, the spleen and liver gradually becoming smaller, and the urine becoming normal with

TABLE II

SUMMARY OF BLOOD EXAMINATIONS OF BABY S.

	TRANSFUSION 2 DAYS OLD ↓	5 DAYS OLD	TRANSFUSION 6 DAYS OLD ↓	15 DAYS OLD ↓ TRANSFUSION	30 DAYS OLD
Hemoglobin	92%	100%	108%	90%	88%
Red blood cells	3,690,000	4,000,000	4,000,000	4,300,000	4,780,000
Color index	1.2	1.25	1.3	1.1	
White blood cells	23,900	20,000	15,400	18,950	
Segmented cells	55%	38%		34%	
Staff cells	8%			8%	
Eosinophiles	3%	2%		3%	
Myelocytes	1%			2%	
Metamyelocytes	1%				
Lymphocytes	21%	56%		45%	
Mononuclears	8%	4%		7%	
Basophiles	1%				
Myeloblasts	2%				
Promyelocytes				1%	
Normoblasts	23,000 c.mm.	400	308	0	
Reticulocytes	18.7%			3.2%	

an absence of both bile and urobilin. He gained weight and on discharge weighed 7 pounds and 3 ounces. At the age of five months he was an apparently normal child, gained weight steadily, and had a normal physical examination.

In this latter case we have an entirely different clinical picture with marked jaundice, urine full of bile, a direct and highly positive van den Bergh reaction, erythroblastosis, and marked reticulocytosis. The high color index and the leucocytosis are features common to both forms of anemia of the newborn.[9, 14, 16] The unusual feature of this case, which must be classified as icterus gravis, is that there was never a significant anemia. This infant was lethargic, eating poorly all the time until the end of the illness, needed fluids administered parenterally, and took months to recover. We are dealing with a subacute disease, usually associated with anemia, instead of an acute anemia of the newborn. It is interesting that so many transfusions were given in the patient with such a high hemoglobin content, which might in part have been due to dehydration. The effects of the transfusions, in contradistinction to the brilliant results attained in the case of anemia without erythroblastosis, were not spectacular. Very interesting and probably of importance, are the facts that after the first transfusion there was no further erythroblastosis, and that the number of reticulocytes dropped almost to normal. It is intriguing to speculate whether the characteristic anemia of the newborn, which so often accompanies icterus gravis, would have developed had not repeated transfusions been given so early and so frequently. At a recent meeting* it was agreed upon by students of the question that transfusion in a case of erythroblastosis can reduce the nucelated red cells to normal figures. This is what seems to have occurred in Baby S., and it is my opinion, supported by others at the meeting, that were it not for the transfusions, Baby S. would most likely have developed the anemia with erythroblastosis so characteristic of icterus gravis. It is quite possible that transfusions aborted this clinical picture, besides being a life-saving measure.

The differential table (Table III) will reveal the differences between the two types of primary anemia of the newborn.

Because of the presence of features common to both forms of congenital anemia, it may be argued that they are different reactions to the same disease. Cases of congenital anemia, or icterus gravis, or universal edema of the newborn have been reported in different babies of the same parents, but never have two of these conditions been reported at one time in one infant.[3, 5] This speaks for a familial character of the disease with its implied constitutional etiology—usually with erythroblastosis as a common feature. The presence of the golden amniotic fluid and orange vernix caseosa at birth in both forms of this

*New York Pediatric Society, February 6, 1935.

anemia argues for an intrauterine etiology. Stransky believes that the etiology is the same, the difference lying in the powers of red cell regeneration. The nonerythroblastic congenital anemia is a type which Finklestein[10] and Stransky[9] have called the aregenerative type. The hematopoietic reaction of infants varies greatly, for in many nor-

TABLE III

		WITH ERYTHROBLASTOSIS	WITHOUT ERYTHROBLASTOSIS
Similar features	Erythroblasts	present	absent
	Color index	high, above 1	high, above 1
	Macrocytosis	marked	marked
	Leucocytosis	high	high
	Premature leucocytes	present	present
	Placenta	large	large
	Vernix caseosa	often deep golden	often deep golden
	Amniotic fluid	often deep golden	often deep golden
Different features	Jaundice	marked	slight, or absent
	Bile in the urine	present	absent
	Bile in the stool	absent	present
	Urobilin production	excessive	normal
	Bilirubin in serum	very high	normal
	Edema	sometimes present	never present
	Viscera	erythropoiesis	no erythropoiesis
	Hemosiderosis	present	absent

mal infants up to two months of age and liver and spleen will show histologic evidences of hematopoiesis. It may thus be that a constitutional difference in erythropoietic capacities determines whether the anemia of a newborn baby, possibly due to the same unknown agent, is characterized by the presence or lack of erythroblasts in the blood and viscera. Whether this is true or not, from a clinical and even from a pathologic point of view, they are two different types of anemia of the newborn.

SUMMARY AND CONCLUSIONS

1. Congenital anemia of the newborn and erythroblastosis are not synonymous.

2. A case is reported of anemia of the newborn without erythroblastosis.

3. A case of icterus gravis is reported without the development of anemia.

4. Transfusion is a life-saving measure in these cases but must be given early and frequently.

5. Transfusions may prevent the development of anemia if given very early in the course of a case of icterus gravis.

6. Erythroblastosis in such a case may disappear after transfusions.

7. A golden colored amniotic fluid and vernix caseosa is an omen of impending congenital anemia with or without erythroblastosis.

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MYASTHENIA GRAVIS IN A CHILD

Observations on the Effect of Ephedrine Therapy

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IN RECENT years interest in myasthenia gravis and certain other muscular disorders has been stimulated by two proposed methods of treatment.

Dr. Harriet Edgeworth,[1, 2] herself a victim of this disease, discovered that she developed increased muscular strength after taking a preparation containing ephedrine sulphate. She demonstrated that the improvement was due to ephedrine by employing it as the sole therapeutic agent and by discontinuing it on seven occasions for experimental purposes. The effect of ephedrine on myasthenia gravis has also been verified by Boothby[3, 4] and by Bayha.[5]

The second approach is closely linked with creatine metabolism and the effect of amino acids upon it. In 1928 Luck[6] found that glycine was the only amino acid which produced an appreciable increase in the amino acid content of muscle. Brand, Harris, Sandberg, and Ringer[7] (1929) showed that the marked creatinuria of patients with progressive pseudohypertrophic muscular dystrophy was further increased after the administration of glycine. They also stated that during glycine feeding there was a decrease in sulphur excretion and that the extra nitrogen eliminated was less than that given as glycine. Adams[8] found no decided change in the nitrogen, phosphorus, or sulphur balance by feeding glycine during a balanced experiment on a patient with myasthenia gravis. Milhorat, Techner, and Thomas[9] (1932) were apparently the first to report clinical improvement in patients with progressive pseudohypertrophic muscular dystrophy after the administration of glycine. They noted, too, an increase in creatinuria when glycine was first given but found that this increase was followed after a time by a decrease in creatine excretion even though glycine was continued. Improvement in symptoms, according to them, was demonstrable during the period of the decreased creatinuria. Boothby[10, 11] and Remen[12] also reported improvement in patients with myasthenia gravis after glycine therapy. From reports in the literature at the present time it would appear that there is less question about the beneficial effect of glycine in patients suffering from myasthenia gravis than there is in those with progressive pseudo-

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hypertrophic muscular dystrophy. Tripoli, McCord, and Beard[13, 14] noted improvement in various muscular dystrophies with glutamic acid as well as with glycine. Boothby[3, 4] has administered ephedrine together with glycine with beneficial results.

While myasthenia gravis is not a common disease at any age, it is rare in children. Following Wilks'[15] first description of this disease in 1877 in a girl whose age was not stated, Campbell and Bramwell[16] in 1900 collected sixty case reports of which four were in children under fifteen years of age. Palmer[17] brought the literature up to date in 1908 and added 126 cases. In six of these the patients were under fifteen years of age. Gerstle[18] in 1929 collected the records of sixty-seven patients from the National Hospital, London, two of whom were under ten years of age and twelve between the ages of ten and twenty years. A few isolated case reports of myasthenia gravis in children under fifteen years of age, since Palmer's collected series, have been made by Booth[19] (1908), Buzzard[20] (1912), Emanuel[21] (1913), Stephenson[22] (1916), Kirsch[23] (1918), Thomson[24] (1919) Adie[25] (1928), and Ziegler[26] (1930).*

A girl, eleven years old, suffering from myasthenia gravis has recently been under our observation. The case is of particular interest because of the response to therapy.

The family attached causal relationship to a tonsil and adenoid operation twelve weeks prior to admission to the hospital but on careful questioning recalled that symptoms were manifested earlier. Initial manifestations were difficulty in swallowing and a change in the character of the patient's speech. For about ten weeks before admission she was bedfast. At the time of the admission she was unable to close her eyes completely. There were also weakness of both sides of the face, paralysis of the soft palate and a weak pharyngeal reflex. The abdominal reflexes and those of the extremities were active, but later marked variability was noted, and at times both superficial and deep reflexes could scarcely be elicited.

Tests revealed weakness of the muscles of the shoulder girdle, back, abdomen, and face. For several days after admission it was necessary to feed the child by stomach tube. At first it was thought that she probably had a postdiphtheritic paralysis. However, the absence of definite improvement after a reasonable time; the marked variability of the symptoms, particularly temporary improvement after rest; and the nature of the symptoms, such as ptosis, facial weakness, difficulty in swallowing, nasal speech, weakness of trunk and extremities, particularly the upper, appeared to warrant the diagnosis of myasthenia gravis. The positive reaction of the muscles to both faradic and galvanic stimulation and a variable, but at times definite, myasthenic response were accepted as confirmatory evidence of such a diagnosis.

During a period of three months the severity of the disease varied. At intervals the patient could be out of bed, but she always tired easily, and she fell on several occasions. She developed pneumonia, and on the third day her respirations became so labored that the advisability of placing her in a respirator was considered. At this time she was given her first dose of ephedrine sulphate (gr. ¼ every six hours subcutaneously). Within twelve hours her breathing was remarkably less labored, the

*This list is collected only from those reports the titles of which indicate the age of the patient and should not be construed as necessarily representing all reported instances of myasthenia gravis in children.

impression being that the medication at least assisted in this. The improvement was progressive for several days, and recovery from pneumonia was otherwise uneventful. The ephedrine was discontinued for a period of eight days, and she returned to a severity of muscular weakness comparable to the degree present at the time of admission. Ephedrine (⅛ gr. t.i.d. orally) was again administered. On the third day there seemed to be slight improvement in her expression. By the fifth day she could close her eyes more completely, and her arm muscles had greater power. With-

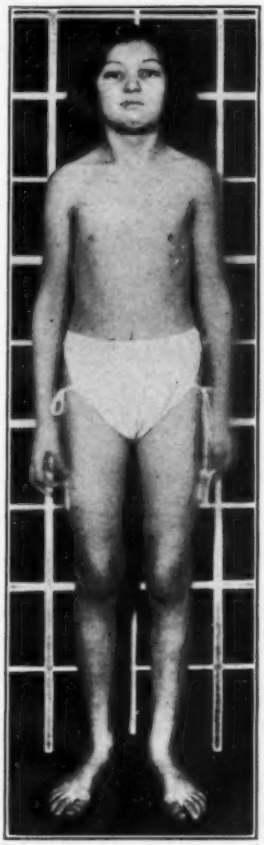

Fig. 1.—Photograph taken before treatment with ephedrine but during a period of remission. Note the apparent effort to hold the head up to compensate for the ptosis of the eyelids.

in another two days her voice had less of the nasal quality. On the tenth day of ephedrine therapy the dose of the drug was increased by ⅛ grain (gr. ⅜ daily) since she had not shown further improvement. This procedure was followed by still further improvement, and twenty days later, after another lull in her progress, the dose of ephedrine was increased to ⅝ gr. per day. Ten days after this, tests revealed markedly increased muscular strength. She could now be up and about and carry on in the hospital school and playroom.

In order to determine more definitely whether this improvement was due to the ephedrine and was not simply a remission of the disease itself and furthermore whether the effect of glycine might be tried, the ephedrine was again discontinued. Within a period of ten days she lost most of the strength recently gained. At this time the administration of glycine was begun in doses of 15 gm. twice a day. This was continued for twenty-three days during which time she became progressively weaker and, although she was permitted to go to the playroom if she chose, she actually spent much of the time in bed. Because of the rapid loss of strength, which was accompanied by an increasing state of mental depression, ephedrine was administered again and glycine discontinued. Within ten days she showed marked improvement and was able to play actively out of doors. She was permitted to return home and a daily dose of ⅝ gr. of ephedrine was continued.

Two weeks later she returned for examination. The parents thought that she had as much or more muscular power as at the time of her dismissal from the hospital, although this varied considerably from day to day. Examination actually revealed rather marked weakness. This was attributed to arising at 4 A.M. in order to make the 75-mile trip to the hospital. Hoping that the good effect of the ephedrine might be augmented, it was advised that 10 grams of glycine per day be given in addition. She returned to her home.

For four days she seemed to be as well as usual. On the fifth day she refused food and drink and remained in bed although the mother insisted that she appeared to have as much strength as usual. During the afternoon she complained of sharp pain in the lumbar region; this later radiated through the abdomen to the groin. During the evening she complained of a generalized "burning-up sensation." The mother stated that by touch she did not appear to have fever. By 3 A.M. she could scarcely talk; shortly after this she became unconscious and died at 9 A.M. The mother, who was sitting at her side, said that the child seemed to be in a natural sleep. No further information as to the cause of death was obtained by a visit to the home and to the family doctor.

COMMENT

In retrospect there appears to be little doubt that the diagnosis of myasthenia gravis is justified. The rarity of myasthenia gravis in children, as well as the variability of the symptoms and the usually insidious onset, may account for delay in recognition in some instances. The most common findings seem to be those involving the muscles of the face and deglutition with resultant ptosis, masklike expression, difficulty in swallowing, and nasal speech. Symptoms of fatigue of the other muscles of the body usually follow, although all muscles are not necessarily involved and different ones may be affected in varying degrees. In some instances, apparently only the muscles supplied by the cranial nerves are involved. The fatigableness and weakness are usually aggravated by use, mental fatigue or strain, and by illness and characteristically are more pronounced in the latter part of the day. There is no reaction of degeneration, the muscles responding normally both to faradic and galvanic stimulation. The so-called "myasthenic response," i.e., progressively weaker muscular responses to repeated faradic stimulation, is often present. Atrophy, except that from disuse, does not occur. Our patient maintained a fairly adequate state

of nutrition and did not have any localized wasting. The course is quite variable, in most instances extending over a long period of time although it may be quite rapid and death may occur in a comparatively short time. Remissions, even over long periods, are a characteristic feature and are likely to make difficult the interpretation of therapeutic procedures.

In the instance here reported the effect of ephedrine appears to be established beyond reasonable doubt as shown by the rapid response during pneumonia when its use actually seemed to be a life-saving measure. The return of marked muscular weakness after its discontinuance on two successive occasions with rapid improvement following its administration again in each instance is additional evidence. This confirms Edgeworth's[1, 2] experience. Complete creatine studies were not performed. However, determinations of creatine and creati-

Fig. 2. Fig. 3.

Fig. 2.—Picture taken several days after the first period of ephedrine therapy. She had lost a small degree of the recently gained strength. This is the third consecutive time of raising the arms above her head. On the eighth trial the height to which she could raise her arms was comparable to that shown in Fig. 3.

Fig. 3.—Photograph taken several weeks after discontinuance of ephedrine and during treatment with glycine. This represents the maximum height to which she could raise her arms at the first attempt.

nine were made before ephedrine was given and several determinations were made subsequently as shown in Table I. If the reaction to ephedrine is manifested by an immediate rise in creatinuria and the improvement in symptoms parallels the decrease in the creatinuria as is stated to be the case after glycine therapy, then the changes in the creatine output ought to be rapid. A marked decrease in creatine excretion did occur in this case about three weeks after the institution of ephedrine therapy. Whether there was a preliminary rise immediately after ephedrine administration unfortunately cannot be stated. No explanation is apparent for the progressive increase in creatine excretion in the last three determinations. Other observations on creatine metabolism in relation to ephedrine should be made.

TABLE I*

DATE	URINARY CREATININE		URINARY CREATINE	
	TOTAL/24 HR.	PER KG./24 HR.	TOTAL/24 HR.	PER KG./24 HR.
3/26/34	479.6 mg.	16.5 mg.	732.6 mg.	25.2 mg.
4/14/34	565.1 mg.	19.4 mg.	261.5 mg.	9.0 mg.
4/15/34	464.9 mg.	16.0 mg.	302.1 mg.	10.4 mg.
4/16/34	490.6 mg.	16.9 mg.	338.5 mg.	11.6 mg.

*Ephedrine was given March 28 to April 2, inclusive, and from April 10 for a period extending beyond April 16. (Determinations were made by Dr. C. C. Wang.)

The experience with glycine administration in this case was not adequate to permit the drawing of conclusions since the benefit is often not apparent for two or three weeks. The child received 30 gm. per day for twenty-three days. During this period there was no improvement, and the child actually became much weaker as demonstrated by Figs. 2 and 3. It is possible, had glycine been continued, that improvement would have ensued. From a practical standpoint continuance of glycine therapy did not seem justified because of the patient's rapid downward course. The planned observation period with the combined use of glycine and ephedrine was unfortunately cut short by her death. It was hoped that we would be able to establish for this patient a minimal therapeutic dose of ephedrine or of ephedrine and glycine. While the amount of treatment necessary is probably to a large extent an individual factor for different patients, more observations with the use of these two drugs are needed. It does not appear to be too much to hope that a "carrying load" may be established for each patient comparable to the use of insulin in diabetes.

SUMMARY

1. A case of myasthenia gravis in a girl, eleven years old, is reported.

2. Marked and rapid improvement in muscular strength was noted after the administration of ephedrine.

3. Neither improvement nor prevention of loss of muscular power was noted after twenty-three days of glycine therapy.

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EFFECT OF TUBERCULIN TEST ON MONOCYTE-LYMPHOCYTE RATIO IN CHILDREN

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THE blood cell response to bacterial invasions is a commonplace of medical knowledge, yet its interpretation from time to time has offered a field for new theories and concepts.

Against invasions by pyogenic microorganisms, the neutrophilic granulocytes form the bulwark of defense. In certain other infectious diseases the nongranular leucocytes, particularly lymphocytes and monocytes, are chiefly mobilized. Thus in pertussis the small lymphocytes increase, whereas in infectious mononucleosis, the large variety is chiefly involved. In tuberculosis and in infection with *B. monocytogenes*, the monocytic system appears to be primarily stimulated. The rapid multiplication of monocytes in rabbits after inoculation with fresh cultures of *B. monocytogenes* (Murray) was so striking that this method was effectively used by Bloom[3] in the study of the origin of monocytes. Likewise, the mobilization of monocytes in experimental tuberculosis of rabbits furnished Sabin and his coworkers[6] a basis for the concept that "tuberculosis is a disease which affects primarily a single strain of cells, the monocytes."

However, it must be added that, while monocytes show evidence of active metamorphosis in tuberculous infection, other cell types are also involved in an equal, if not greater, degree of activity. Previous to the publication of observations by Cunningham, Sabin, Sugiyama, and Kindwall,[6] a significant contribution on the cellular reaction in tubercle formation was recorded by Maximow.[14] In his culture of mammalian tissue in the presence of tubercle bacilli, Maximow observed the transformation of histiocytes into polyblasts and thence into epithelioid and giant cells. He also emphasized the active rôle played by the lymphocytes in the formation of tubercle. Basing their observations on the study of the embryonic histogenesis of blood and connective tissue, Maximow and later Alfejew[1] have further shown the close genetic relationship existing between the lymphocytes and the histiocytes. Clinical examination of the peripheral blood in cases of human tuberculosis also bears out the fact that lymphocytes as well as monocytes participate actively in the defense mechanism against in-

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fection. Thus, a true evaluation of the cellular activity in tuberculosis must be based, not alone on the study of monocytes, but also on the nature of lymphocytic variations.

The interrelation of monocytes to lymphocytes in the clinical evaluation of tuberculous process was first set forth by Cunningham and Thompkins[7] who considered the monocytes to be an index of the tuberculous invasion, and the lymphocytes an index of resistance. They suggested the monocyte-lymphocyte ratio as a mathematical expression of these two processes. Reports confirming this hypothesis have since been published by Morriss and Tan,[17] Rogers,[20] Camp and his coworkers,[5] Flinn and Flinn,[10] Blackfan and Diamond,[2] Finner,[8] Smith,[21] and Hamil.[11]

In addition to the changes in monocytes and lymphocytes in tuberculosis, Medlar[15, 16] introduced a concept that neutrophilic granulocytes are also intimately involved in this disease. He found that an increase of granulocytes occurred whenever the primary tubercle passed into the caseous and necrotic stage. Even after ulceration and cavitation of the lesion, the neutrophile count may remain elevated until the process has completely healed. Thus he regarded the three types of leucocytes as representing three processes or stages of the tuberculous lesion: namely, monocytosis during the active stage of tubercle formation; granulocytosis occurring in caseation and cavitation; and lymphocytosis associated with the healing process. On the basis of this theory, Flinn[9] analyzed 1,000 routine differential counts on fixed smears of tuberculous patients and found the following average values for monocyte-lymphocyte and lymphocyte-neutrophile ratios:

Class of Patients	*M:L*	*L:N*
I. Minimal	1:16.75	1:1.53
II. Moderately advanced	1:15.78	1:1.75
III. Far advanced	1: 8.18	1:2.50
IV. Very far advanced	1: 4.77	1:3.61

The conclusion reached by this observer was that a decreasing M:L ratio and an increasing L:N ratio pointed definitely to a more active and extensive lesion, while the converse indicated just as definitely improved lung conditions.

Similar changes in monocyte-lymphocyte ratio have been observed after the application of tuberculin skin tests (Hamil[11]) and also in the progress of treatment with tuberculin (Pinkhof[19]). Hamil found that in miliary and severe active tuberculosis, there were no demonstrable changes. However, in chronic tuberculosis of the bone and healing or healed pulmonary and glandular tuberculosis, he found that the application of a tuberculin test caused a decrease in monocyte-lymphocyte

TABLE I

TUBERCULIN-POSITIVE CASES WITH RISE IN M:L

CASE		SEX	AGE IN YR.	B	1	2	3
1	B. G.	F	14	0.16	0.50	0.33	0.11
2	R. S.	M	4	0.12	0.34	0.20	
3	P. G.	M	9	0.04	0.36	0.76	0.16
4	F. W.	F	2	0.04	0.32	0.11	
5	J. D.	M	12	0.04	0.41	0.52	0.40
6	E. G.	M	9	0.18	0.38	0.37	0.19
7	H. G.	M	9	0.20	0.43	0.48	
8	R. O.	M	1	0.10	0.26	0.24	
9	G. O.	M	13	0.12	0.32	0.50	0.20
10	D. S.	M	8	0.12	0.40	0.13	0.20
11	W. B.	M	2	0.05	0.18	0.15	0.11
12	W. M.	M	7	0.19	1.00	0.38	
13	J. S.	F	5	0.12	0.31	0.10	
14	P. D.	M	5	0.07	0.20	0.40	
15	E. S.	M	11	0.25	0.38	0.41	
16	W. R.	M	6	0.03	0.53	0.40	
17	B. T.	F	9	0.14	0.35	0.22	
18	F. R.	F	13	0.38	0.43	0.28	
19	F. H.	M	13	0.04	0.17	0.50	0.35
20	W. G.	M	5	0.11	0.40	0.12	
21	M. M.	F	7	0.09	0.26	0.14	
22	R. N.	M	13	0.08	0.59		
23	A. M.	M	4	0.01	0.10		
24	D. E.	M	5	0.12	0.15	0.23	
25	J. B.	M	14	0.04	0.15	0.40	
26	D. B.	F	14	0.02	0.21	0.43	
27	G. G.	M	12	0.06	0.43		
28	F. K.	M	10	0.18	0.33	0.28	0.30
29	R. T.	M	8	0.15	0.34	0.17	0.30
30	F. W.	M	12	0.08	0.17	0.63	
31	C. G.	M	7	0.09	0.09	0.43	0.18
32	D. C.	M	7	0.05	0.17	0.11	
33	L. F.	M	14	0.07	0.36	0.30	
34	A. M.	F	9	0.14	0.18	0.28	
35	R. A.	M	12	0.29	0.37	0.17	
36	M. K.	F	10	0.14	0.15	0.31	0.22
37	E. R.	M	6	0.10	0.42	0.27	
38	C. G.	M	8	0.27	0.30	0.19	0.30
39	J. W.	M	5	0.14	0.30		
40	F. K.	F	13	0.14	0.33	0.35	
41	M. S.	M	11	0.06	0.16	0.20	
42	R. Z.	F	3	0.25	0.51	0.83	0.57
43	R. K.	M	2	0.11	0.49	0.57	0.39
44	P. C.	F	9	0.10	0.33	0.21	
45	J. N.	F	10	0.06	0.15	0.23	0.13
46	D. K.	F	5	0.07	0.41		
47	A. B.	F	12	0.23	0.25	0.20	
48	M. H.	F	13	0.66	0.74	0.62	0.26
49	D. G.	F	15	0.15	0.21	0.16	
50	A. H.	F	11	0.08	0.25	0.34	0.10
51	G. O.	F	10	0.08	0.37	0.29	
52	J. M.	F	15	0.11	0.66	0.33	
53	B. M.	F	13	0.23	0.61	0.32	

ratio. His data, however, were based on blood examinations made at irregular intervals, hence they are not sufficiently complete for deductions.

For the purpose of determining whether or not application of tuberculin tests produces significant changes in the blood picture comparable to those seen in various stages of tuberculosis, the total and differential counts were made on eighty children before and after the tests. Sixty-three cases showed positive tests in varying degrees, while seventeen were negative. The intracutaneous method (Mantoux) of application was followed, the routine dosage being 0.1 c.c. of a 1:1,000 dilution of old tuberculin. In a few cases 0.1 c.c. of a 1:100 dilution was used. The blood was first studied just before the test, then at the height of the reaction (from forty-eight to seventy-two hours) and again one to two weeks thereafter.

These three fixed intervals of blood study constituted the routine examination for the majority of tuberculin tests applied. In a few cases, convenience and indications dictated more or fewer blood counts at intervals deviating somewhat from the normal routine. The resulting data are divided into three series and presented in tabular form (Tables I to III).

Table I gives the values of the monocyte-lymphocyte ratio in fifty-three children who gave positive tuberculin tests of varying degrees. In all these cases the total number of monocytes rose at the time of reading. In the majority of cases, the most decided elevation was noted forty-eight hours after the application of the test. A number of cases, however, showed but a slight rise at forty-eight hours, the decided elevation not occurring until a few days later. In these latter instances, the total monocyte count continued climbing for several days after the application of the test, gradually falling to the original level in the course of one to two months. One strikingly constant feature of this group, however, was the increase in monocyte-lymphocyte ratio. This rise in the ratio, however, showed a great variation, ranging from the minimum increase of 0.01 (Case 36) to the maximum of 0.81 (Case 12). The ratio in Case 36, which showed the smallest amount of elevation, continued to climb during the following few days, resulting in a gain of 0.17 at the end of the week. The ratio in Case 12, showing the largest value of increase, dropped sharply to a comparatively low level in one week following the test. The average gains in monocyte-lymphocyte ratio of this entire group at two intervals after the application of the test are as follows:

Intervals	*Average M:L*	*Average Gain*
Before application	0.13	
48-72 hours (53 cases)	0.35	0.22
5-14 days (42 cases)	0.32	0.19
1-6 months (15 cases)	0.28	0.15

The above analysis confirms the finding that the initial ratio of 0.13 is well within the normal limits, according to the standard curve of monocyte-lymphocyte ratio previously published. This average ratio more than doubles after the application of tuberculin tests and remains elevated for variable lengths of time, with a subsequent tendency to gradual decline.

When this alteration in monocyte-lymphocyte ratio is analyzed as to its underlying factors, it is seen that, while the monocytes are increased in both relative and absolute numbers, the elevation of the ratio is also brought about by a decrease in the number of lymphocytes. The granulocytes usually show very little and inconstant change after the tuberculin test is applied. Therefore, the apparent rise in the granulocyte-lymphocyte ratio is caused, not by the increase in granulocytes but rather by the decrease in lymphocytes. Clearly, therefore, the index of reaction to injection of tuberculin is gauged more correctly by the change in the monocyte-lymphocyte rather than granulocyte-lymphocyte ratio.

Table II gives the results of blood examinations in ten positive tuberculin reactions, showing a slight decrease in monocyte-lymphocyte ratio. The changes in this ratio are summarized as follows:

Intervals	*Average M:L*	*Average Loss*
Before application of test	0.31	
48-72 hours	0.17	0.14
1-2 weeks	0.16	0.15

It is to be noted that the average initial monocyte-lymphocyte ratio in this group is higher than the normal value (0.15). Therefore, the decrease of 0.14 and 0.15 at two intervals appears of little significance.

The two tables of results reveal that in a total of 53 positive tuberculin tests, 84.2 per cent show a decisive increase in monocyte-lymphocyte ratio at forty-eight to seventy-two hours, while 15.8 per cent show a slight decrease.

TABLE II

TUBERCULIN-POSITIVE CASES WITH FALL IN M:L

CASE	SEX	AGE IN YR.	B	1	2	CASE	SEX	AGE IN YR.	B	1	2
1 B. K.	M	9	0.53	0.27	0.15	6 L. F.	M	5	0.37	0.25	0.21
2 D. J.	M	4	0.30	0.14	0.14	7 O. C.	M	8	0.15	0.14	0.23
3 R. D.	M	6	0.48	0.16	0.22	8 W. T.	M	15	0.61	0.36	
4 L. L.	M	7	0.19	0.15	0.05	9 M. N.	F	4	0.13	0.11	0.18
5 A. E.	F	6	0.30	0.16	0.14	10 G. M.	F	7	0.21	0.13	0.27

Table III gives similar data on a group of seventeen children with negative tuberculin tests. The monocyte-lymphocyte ratio shows a slight increase in the first six cases, while the remaining eleven all

show a decrease. The average initial ratio is 0.22, which is slightly higher than the normal value. The average decrease in 11 cases is 0.08, and the average increase in six cases is also 0.08. Only a few of this group returned for the third time, apparently because of the absence of clinical indications; hence the majority of data covers only the two initial blood examinations. Although this negative group is far too meager to serve as a control, it must be emphasized that in this series the changes in monocyte-lymphocyte ratio are significantly negligible.

TABLE III

TUBERCULIN-NEGATIVE CASES

CASE	SEX	AGE IN YR.	B	1	2	CASE	SEX	AGE IN YR.	B	1	2
1 S. R.	F	9	0.14	0.20	0.16	10 J. D.	M	9	0.28	0.13	
2 L. S.	F	6	0.37	0.38		11 E. S.	F	11	0.19	0.08	
3 A. L.	F	9	0.09	0.14	0.12	12 P. P.	M	4	0.38	0.16	
4 W. H.	M	8	0.04	0.18		13 J. S.	F	2	0.27	0.12	0.19
5 W. G.	F	14	0.26	0.75	0.11	14 D. G.	F	10	0.32	0.17	0.17
6 J. G.	M	9	0.05	0.19		15 W. G.	M	8	0.23	0.13	0.16
7 J. S.	F	3	0.32	0.30	0.09	16 G. H.	F	10	0.07	0.03	
8 M. R.	F	1.5	0.12	0.10	0.08	17 R. I.	M	10	0.27	0.18	
9 T. B.	F	11	0.37	0.17							

SUMMARY AND CONCLUSIONS

The blood cell changes following the application of intracutaneous tuberculin test (Mantoux) in eighty children are reported. Of these, sixty-three were cases of positive reaction, and seventeen were negative.

Fifty-three children of the positive group (84.2 per cent) showed an increase in monocytes and a decrease in lymphocytes following the tests, giving a definite rise in the monocyte-lymphocyte ratio. In the remaining ten children of this group (15.8 per cent), this ratio diminished.

In the seventeen negative reactions, changes in the monocyte-lymphocyte ratio were inconstant. A small percentage of this group showed a slight increase in ratio, the majority definitely decreasing. This slight increase in the negative reactions is negligible as compared with that of the positive group.

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Pediatric Clinics

THE HEIDELBERGER KINDERKLINIK

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THERE is little to be said concerning the construction and organization of the Heidelberger Kinderklinik. It is a hospital for children similar to every other one. It has a bed capacity of 200 and consists of a group of five buildings (main building, infant station with diet kitchen, out-patient building, a pavilion for infectious disease, and laundry) situated in a large garden. Its only claim to fame is that it is a venerable institution. That it is old comes from the date of its founding, and that it is worthy because from the smallest conceivable beginnings it has slowly but continuously developed step by step into its present-day form.

The institution was founded July 1, 1860, by Prof. Dr. Theodor von Dusch, with six beds in a rented house. He was aided in the medical work by a certain Dr. (later Professor) Oppenheimer. The nursing personnel consisted of a supervisor with a maidservant. After two years the number of beds was increased to nine, one of which was borrowed. In 1867 a small house was obtained in Bunsenstrasse. Five rooms were used, the remainder of the house of necessity being rented out. It was not until 1885, twenty-five years later, that its own building was erected on the site where the hospital stands today. After fifty-five years the institution finally underwent material expansion in the form of the stately new buildings erected in 1914. It needs neither great mathematical nor historical talent to discover that the Heidelberg children's clinic celebrates this year a double jubilee—or, more correctly stated, should celebrate the seventy-fifth year of its founding and the fiftieth year of its existence on the present site. Since I am no friend of festivities, I will, recalling the beautiful motto of its founder, "In stetiger Arbeit ernst, prunklos, and treu," call no one's attention to this and hope for the strongest discretion on the part of my American colleagues.

Like the majority of children's hospitals in Germany and Austria the institution was founded as a purely charitable institution. For this reason, as is customary with organizations which depend almost exclusively upon public benefactions, the balance each year showed a deficit. This deficit with our institution became always larger and larger and at times reached a considerable amount. But in the end this "Sorgenkind" of the city of Heidelberg was always taken care of despite all calamities, and the steady progress was not retarded.

This happy fact is chiefly due to the Grand Duchess Louise of Baden, who took the hospital under her protection, at the request of the directors, on July 29, 1864, and permitted the Heidelberg children's hospital to assume the honored name of "Luisenheilanstalt," which it has now borne for more than seventy years with the deepest appreciation. With this step the institution became at once extremely popular. If anyone—even today—asks in Heidelberg, "Where is the university children's clinic?" he will rarely ever receive a satisfactory answer. Most will reply with the question, "Do you mean the Luisenheilanstalt?" Indeed the Luisenheilanstalt

is known to everyone not only in the community where it carries on its activities, but throughout the Badische country. One must recall the general popularity and esteem in which the Princess was held at that time in order to understand the numerous legacies, free beds, and gifts of all kinds that have been so generously bestowed upon the Luisenheilanstalt. However, there are always debts. These are taken care of through public organizations, above all from all the profits accruing from the "Luisen Bazar," an event of importance in the social life of Heidelberg.

In 1920 the Luisenheilanstalt suddenly found itself with a debt of many millions of marks as a result of inflation (on account of the failure to pay a coal bill at the right time). All bequests and legacies became at one time worthless. In this crushing crisis the hospital was completely taken over by the city. In a strict sense it first became at this time a university children's clinic. Previously the relation with the government was so arranged that the honorary director of the Luisenheilanstalt,

Luisenheilanstalt. (Photograph by Max Kügel.)

in the form of a personal union, functioned as professor of pediatrics in the university, and the hospital received regular financial help and special grants from the university authorities in view of its importance for teaching.

The following have served as directors of the clinic:

Prof. Th. v. Dusch, 1860-1889
Prof. O. Vierordt, 1889-1906
Prof. E. Feer, 1906-1911
Prof. E. Moro, since 1911.

Professors v. Dusch and Vierordt were directors of the medical polyclinics and had charge of the Luisenheilanstalt only as an additional function. After Vierordt's death in 1906 a professorship in pediatrics was established, and Professor Feer inducted. He was thus the first director of the children's clinic. In 1919 Professor Moro, the successor of Feer, was named ordentlicher professor.

This gradual separation from internal medicine reflects in a striking way the development of pediatrics in Germany. Historically it is noteworthy that in 1902 the Heidelberg children's clinic was one of the first to establish a large infant welfare station, after the pattern of Schlossmann's organization, supplying nursing care and a diet kitchen for the needy infants of the city. In this building were glass partitions for the separation of the rooms; these are supposed to be the first of their kind. I can give no guaranty for the correctness of this, but in showing the well-lighted building to foreign guests, I am accustomed to point out this historical fact.

Another somewhat old-fashioned feature of the Heidelberg children's clinic is its surgical division, which in its arrangement meets the most modern demands. The older children's hospitals were all arranged in this way, and surgical as well as medical cases were admitted, the operations being performed by a staff physician attached to the hospital. I have tenaciously held to this tradition in spite of all modern trends and every conceivable kind of opposition. In this way there not only remains a constant contact with the important borderline surgical field, but furthermore it gives the hospital physicians the much needed opportunity to observe surgery in children, if only as observers and students. Finally, what is most important, the children who have been operated upon, and particularly the infants, are nowhere else so well cared for and treated as in a modern children's hospital.

With the striking upswing in social welfare in the last few decades, the sphere of the hospital rapidly increased beyond the limits of its original conception. Since 1902 it has served not only for the care and treatment of sick children, clinical instruction, the training of pediatricians and for research, but it has become the central institution of public child welfare work for the city and district of Heidelberg. Especially noteworthy is its training school for children's nurses, which has grown from year to year in attendance. Each year approximately fifty children's nurses are trained and prepared for the government examination held twice a year in the hospital.

The number of papers which have been published from the Heidelberg clinic under my directorship amount to over four hundred. I will mention in particular the basic studies of Freudenberg and György on rickets, tetany, and the vitamins. Finally, on account of its historical interest, attention may be called to the fact that from the Luisenheilanstalt came the discovery and first description of thrombopenia in Werlhof's disease by Brohm (1881), and the important studies concerning congenital pyloric stenosis by Ibrahim (1902) at that time an assistant under Vierordt in the Luisenheilanstalt.

Critical Review

NEUROLOGIC CONDITIONS IN INFANTS AND CHILDREN

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THE purpose of this review is to call attention to the neurologic complications which may occur in infants and children with some of the common contagious diseases. In addition, the literature pertaining to this phase of the disease is reviewed and descriptive case histories of some of the patients who have been treated at the Infants' and Children's Hospitals of Boston with such disturbances are presented.

The incidence of neurologic complications occurring in the course of *morbilliform measles* is difficult to determine, as the literature contains very little information in regard to this phase of the disease. Ker[1] reports one case of transverse myelitis in 12,000 consecutive cases of measles; Boenheim[2] has noted neurologic complications in per cent in 5,940 patients; Shamberg and Kolmer[3] simply state that "paralysis following measles is a rare complication"; Holt and McIntosh[4] in their latest edition give a brief discussion of the subject but do not mention the incidence. Allyn[5] was able to collect 41 cases, 35 of which had developed palsies of cerebral origin; recently Ford[6] has collected 113 cases from the literature and added 12 of his own. In view of the fact that 95 per cent of the population contract measles, it at once becomes apparent that complications involving the central nervous system are rare. Nevertheless, during the past few years, an increasing number of case reports have been recorded[7-16] dealing with both the clinical and pathologic aspects of this complication.

In those instances in which *encephalitic complications* develop during the course of the disease, the symptoms usually manifest themselves on the third or fourth day after the appearance of the rash. In the thirteen cases reported by Peterman and Fox,[11] evidence of central nervous system involvement appeared between the second and eighth day following the development of the exanthem; the majority, however, developed symptoms on the fourth day following the appearance of the rash, and this has been the period noted by most observers.

The symptoms of this type of central nervous system involvement are usually initiated by either drowsiness or convulsions and then fol-

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lowed by stupor. As a rule, there is a sudden elevation of temperature at this time. Muscular rigidity and twitchings are typical of this stage. The patient usually remains in a comatose condition for the following three to four days, at the end of which time consciousness gradually returns, and an uneventful recovery is made. However, the stupor may become prolonged and may be accompanied by a great variety of central nervous system manifestations, some of which frequently produce changes of an irreparable nature.

Transverse myelitis and *peripheral neuritis* are seldom encountered as they occur less frequently than do the encephalitic complications. Miller and Ross[17] reported the case of an eleven-year-old girl who, during the course of measles, developed pain and tenderness on deep pressure over the spine in the upper lumbar region. During the succeeding seven days, the pain became more pronounced and was accompanied by paresis of both lower extremities with loss of reflexes and rectal and vesicle sphincter control. Over a period of two and one-half years there was a gradual recovery. Similar cases have been reported by Box,[18] Bergenfeldt,[19] Erb and Morgan,[20] McCausland and McClendon,[21] La Passo,[22] and Morton.[23] Ascending myelitis has been reported by Ellison;[24] Williams[25] has called attention to a case of disseminated sclerosis developing in a three-year-old girl on the fourth day of her illness. Crockford's[26] patient developed typical signs and symptoms of encephalitis, and, after the acute phase of the disease had subsided, the resulting clinical picture closely simulated that of paralysis agitans. Polyneuritis simulating that seen after infectious or toxic conditions has been noted by Roche.[27]

Although complete recovery may occur, yet in the majority of instances *the prognosis* must be guarded. In the twelve cases reported by Neal and Applebaum,[10] there were three deaths, and, of the remaining nine children, one has petit mal, and one is mentally defective. Ford's[6] statistics (125 cases) show complete recovery in 25 per cent, death in 10 per cent, and residual symptoms in 65 per cent. Seven patients have been treated at the Infants' and the Children's Hospitals of Boston, and of this group five show no evidence of sequelae, one is feebleminded, and another is now encountering difficulties in school as a result of inability to concentrate upon the class work. Of Peterman and Fox's[11] group, complete recovery occurred in six patients; five died during the course of the disease; another died from pneumonia; and one is mentally retarded.

The chemical and cytologic changes in the *cerebrospinal fluid* are not characteristic of the disease as they stimulate those seen in any of the usual forms of encephalitis. The pressure is increased; the fluid is clear; and both sugar and globulin are present. The cells, the majority of which are of the lymphocytic series, are usually increased in

number, the total count varying between 8 and 200 per cubic millimeter although occasionally counts as high as 800 per cubic millimeter have been observed.

Although various procedures have been employed, at the present time there is no specific form of *therapy*. Convalescent measles serum has been administered intravenously, intramuscularly, and intraspinously to some patients,[11, 13] and in certain instances it has been thought that improvement followed this form of treatment. However, the number of patients so treated is too small to warrant any conclusions, and, as Andrews[28] has pointed out, once the biologic union has been made between a virus and a cell such treatment is not effective. (One has only to recall the present status of convalescent poliomyelitis serum in the treatment of the acute preparalytic stage of poliomyelitis to be skeptical.[29, 30]) Symptomatic measures, with special attention to those which may reduce increased intracranial pressure, may prove to be of value in some instances.

Necropsy studies have shown rather constant abnormalities. Congestion and hemorrhages are the most common findings, although perivascular demyelinization is perhaps the most characteristic change seen in the disease.[31, 32] In view of similarities in the pathologic changes observed within the central nervous system, van Bogaert[33] has raised the question as to whether or not these changes are not the result of an allergic reaction in an individual who has not developed immunity to the disease; he has also suggested that the changes might not to be due to the virus of measles at all, but to some other virus that is a normal habitat of the respiratory passages and, as a result of the infection, has assumed virulent and neurotrophic characteristics. This latter view is supported by Greenfield[34] who states that "Both the postvaccinal and other forms of encephalitis which follow eruptive fevers are not directly due to the virus of the preceding fever, but to another virus which is either stimulated to activity or is directed against the nervous system by the exanthem." Léchelle, Bertrand, and Fauvert[35] have opposed this view and, on the basis of their studies which have shown perivascular hemorrhages and congestion to be the chief features, are of the opinion that at present the knowledge of the biologic reactions of virus is not adequate to justify any conclusion. By means of encephalography McCausland and McClendon[21] were able to demonstrate the presence of dilated ventricles and deepened subarachnoid spaces seventeen days after the onset of central nervous system manifestations. This would suggest that atrophy of brain structure occurs at an early date.

Photographs and case abstracts of some of the patients who have been treated at the Infants' and the Children's Hospitals of Boston are appended.

Epidemic parotitis, or mumps, may at times produce profound changes within the nervous systems of infants and children. The degree and the severity of the resultant symptoms vary from mild and transient periods of headache to evidences indicative of a severe meningoencephalitic reaction. These disturbances may appear not only before, during, or after the glandular involvement, but may even occur in the absence of enlargement of the parotid, submaxillary, or sublingual glands. In the majority of instances, however, the symptoms of a central nervous system reaction appear during the height of the parotitis and are then present for from three to ten days. Voison,[36] Colomb and Mercier,[37] Casparis,[38] and Walker[39] have all reported instances in which the parotitis did not appear until several days after the development of symptoms referable to a disturbance within the central nervous system; Peterman[40] has recently reported two typical cases of mumps meningitis occurring in twins, neither of whom presented the usual clinical evidence of mumps. In a series of eleven patients suffering from mumps meningitis who have been treated in this clinic, five did not develop apparent enlargement of the salivary gland either while at home or while within the hospital. Therefore, it would appear that the time of onset of meningeal disturbances bears no relationship to either the stage or severity of the parotitis but is dependent directly on the invasion of the central nervous system by the infectious agent. The variability in the time of the development of the symptoms and the recognized fact that evident parotid enlargement may not be present necessitate that one should always entertain the possibility of this disease whenever encephalitis is being considered.

The earliest evidence of central nervous system involvement is usually a sudden elevation in temperature associated with the development of headache and vomiting. Not infrequently these symptoms may mark the height of the disturbance and, after persisting for three to four days, completely disappear. In contradistinction to these mild manifestations, the onset may be abrupt and the clinical course stormy. The patient may complain of severe headache, begin to vomit, and then have one or more convulsions followed by delirium, stupor, or coma. The variability in the severity of the disorder is exemplified in two cases reported by Casparis;[38] one, a boy seven years old, had been perfectly well, when suddenly he complained of a headache and a chilly sensation. During the following forty-eight hours, he enjoyed good health, but on the third day his temperature rose to 102° F., and he had a generalized convulsion which was followed by delirium and stupor. (Parotitis was not evident until eighteen hours after the onset of these symptoms.) The other patient was a child eight and one-half years of age who complained of headache and vomiting and had a temperature of 102° F. On account of suggestive nuchal rigidity a

diagnostic lumbar puncture was performed, and a characteristic cerebrospinal fluid was obtained; twenty-four hours after admission the patient developed bilateral parotid swelling. In both of Wesselhoeft's[41] patients the onset was abrupt with convulsions, coma and elevated temperature. Physical examination reveals such signs as stiff or retracted neck, exaggeration of the deep reflexes, and positive Kernig and Bakinski signs. Ankle clonus and tache cérébrale may be demonstrated, although they are often not present. Pain can usually be elicited if efforts are made to flex the neck anteriorly, and at times there may be definite rigidity of the spine. These observations, when taken into consideration with the inability of the patient to flex the neck anteriorly, may result in a preliminary diagnosis of acute anterior poliomyelitis.

The duration of the symptoms of meningeal disturbance is variable, and, although they usually persist from three to ten days, they may last for several weeks as in the patient, reported by Dumitresco, Jonnesco, and Chiser,[42] who remained in deep coma for twenty-one days. The average duration of symptoms in the eleven patients herein referred to was from four to nine days.

The alterations that may occur in the *cerebrospinal fluid* are not pathognomonic of this disease as they do not differ from those changes that have been observed in other forms of encephalitis. The fluid is usually under increased pressure, is water clear or slightly ground-glass in appearance, contains globulin and therefore yields a positive Pandy's test, contains reducing substances in normal amounts, and when examined bacteriologically yields no organism. Associated with these changes, there is usually a pleocytosis, the majority of the cells belonging to the lymphocytic series. The type of cells present is predominantly of the mononuclear series, yet during the first few hours of the disease there may be an equal distribution between polymorphonuclear leucocytes and lymphocytes, or there may be only cells of the former type. The recognized fact that the type of cells present in the cerebrospinal fluid tends to change with the duration of the disease would explain the different observations that were made by Dopter[43] and Lavergne,[44] the latter reporting an equal distribution between polymorphonuclear leucocytes and lymphocytes and the former reporting only polymorphonuclear leucocytes. As can be seen from the accompanying table, the total cell count may vary within wide limits, some cases showing only a mild cellular reaction, while others show a marked response. In the majority of instances the total cell count is usually over one hundred. In Casparis'[38] cases the initial counts were 470 and 900, respectively; in Wesselhoeft's,[41] 1,420 and 570; and in the cases reported by Weissenbach,[45] counts as high as 1,000 were not unusual.

The cell count of the cerebrospinal fluid remains elevated for a variable period of time after all clinical evidence of meningeal irritation has disappeared. Casparis noted increased counts as late as the thirty-sixth and forty-first days, while Chaufford and Boidon[46] presented cases that showed a pleocytosis at even a later date. In the majority of instances there is not sufficient *clinical evidence* of meningeal irritation in these patients to warrant repeated lumbar punctures over a prolonged period of time, and for this reason the exact duration of the pleocytosis has not been determined. Weissenbach, Basch, and Basch[47] concluded from their studies that the cell count is reduced to fifty or below within ten days from the onset of the symptoms, and that from that time on there is a very slow return to normal.

The *frequency* with which involvement of the central nervous system is detected in association with mumps must of necessity vary according to the signs and symptoms which each observer may consider as indicative of such involvement. Thus recurrent headache of a more or less severe nature, either with or without associated vomiting, may by one individual be considered as evidence of an early meningeal disturbance, whereas another observer may assume that the reactions are simply the natural responses of the patient to the presence of an acute infection and that they do not necessarily signify the involvement of the central nervous system. Nor can the chemical or cytologic alterations within the cerebrospinal fluid be considered as conclusive evidence of meningeal involvement, as the results of the studies of various observers are not in entire agreement. Thus Dopter[48] in 1910 stated that there was evidence of meningeal involvement in 9.8 per cent of 1,750 cases; Haden[49] observed changes in nine among 475 patients; in 5,756 cases of mumps occurring at Camp Wheeler, Radin[50] observed "convulsions" in one patient, but no other definite signs of central nervous system involvement; Wesselhoeft[41] has recorded two cases of meningoencephalitis among 824 patients, and Massary[40] found no evidence of nervous system involvement in a series of 1,135 patients.

Prognosis.—The prognosis in mumps meningitis is usually very good, as only occasionally does one encounter sequelae. If one is to judge from the cases reported in the literature and the eleven additional cases in this group, it would appear that neither the severity of the onset nor the degree of changes within the cerebrospinal fluid, either cytologic or chemical, can be considered as of prognostic significance. However, complications of a rather severe nature have been reported. Sicord[51] has reported a case of hydrocephalus following mumps meningitis; Sorel,[52] a case of aphasia that persisted for fifteen months; and Findlay,[53] a case of hemiplegia that was present for a considerable period. Store and Chiser[54] have also reported a patient with dementia, diplegia, and athetosis.

When one considers that death from mumps meningitis is extremely rare, it at once becomes apparent that information concerning the nature of the *pathologic process* must be limited. Maximovitch[55] in 1880 was the first to describe the postmortem observations in this disease; he observed that the brain was edematous, that the sulci were filled with a serofibrinous exudate, and that there was marked hyperemia of the pons and cord. This was the first suggestion of the true nature of the disease, and naturally numerous theories were advanced in an effort to explain these observations. The first suggestion that the pathologic process was that of an encephalitis was made in 1898 by Gallavardin,[56] and subsequent studies have confirmed his impression. Larkin,[57] in 1919, reported two cases with autopsy studies and demonstrated the presence of a diffuse serosanguineous meningoencephalitis. Gordon[58] has studied four autopsies, all of which showed a moderate meningeal congestion, while two showed definite flattening of the convolutions. In none of the four cases was he able to demonstrate the infiltrative lesions involving the cortex or spinal cord which are so characteristic of poliomyelitis.

A study of the eleven cases from this clinic in which a diagnosis of mumps meningitis was made shows that these patients may be divided into two groups: namely, (1) those cases in which the meningeal symptoms were accompanied by parotitis, and (2) those cases in which the meningeal symptoms were *not* accompanied by recognized parotitis. It is in this latter group that difficulty was encountered in establishing the diagnosis, and frequently it could be made only presumptively and on evidence such as a history of definite or intimate exposure to a nonimmune individual known to be suffering from mumps; or to the presence of some other complication such as orchitis, mastitis, or nephritis which could be attributed to the disease. In certain instances even this evidence was absent, and, as a result, the diagnosis could not be made definitely.

Among the other neurologic conditions that may occur in association with mumps is the involvement of the *spinal cord*. This condition is extraordinarily rare, and only one case report with survival has appeared in the literature.[59] This patient was a girl sixteen years of age, who, twelve days after the onset of mumps and when she had apparently recovered from her illness, resumed her usual activities. Two days later she complained of weakness in her lower extremities and had to be catheterized; on the fourth day there was complete flaccid paralysis of the trunk and lower extremities with absent reflexes, relaxed rectal sphincter, and distended atonic bladder. Further examination showed complete cutaneous anesthesia to all forms of sensation on the inner aspect of the arms and below the second intercostal space. The cerebrospinal fluid was under 8 cm. of mercury

pressure, was clear, and contained both sugar and globulin (200 mg.). Cytologically there were only three cells, all of which were of the lymphocytic series. Bacteriologic study revealed no further information. When she was reexamined six months later, there was no improvement in her physical condition. The sharply demarcated, and also complete, anesthesia, the paralysis, the increased protein of the cerebrospinal fluid, and the subsequent clinical course of the patient would appear to justify the diagnosis of myelitis, probably transverse, in this patient. Warrington[60] has described a child who, ten days after the development of parotitis, developed the signs and symptoms of an ascending myelitis (with flaccid paralysis, anesthesia, etc.) which finally involved the diaphragm and resulted in death.

Perhaps one of the most distressing, and certainly one of the permament, complications is *deafness*. This condition, which may occur at any time during the course of the disease, usually appears within four days after the onset of mumps and is frequently preceded by tinnitus or vertigo. The deafness, which is total and permanent, has been attributed by some writers to the development of a basal meningitis although the more commonly held view is that it is the direct result of damage to the labyrinth, i.e., a true labyrinthitis. In one study of eight cases, three were found to have changes in the middle ear only, one in which the cochlea and semicircular canals were involved, and three in which the internal ear alone was involved.[61] Hubbard,[62] who has made a detailed study of this disturbance, states that mumps may be given as the cause of deafness in from 3 to 5 per cent of deaf mutes in the United States. He states further that many cases of hypacusis of unknown or indefinite origin may easily be the result of mumps.

Peripheral Neuritis.—In very severe cases of neuritis there may be paralysis of all the extremities accompanied by loss of all tendon reflexes. Nemlicker, Chernikov, and Solomonowa[63] have recently reported three patients, two adults and one boy, who, during a mild epidemic of parotitis, suffered from diffuse polyneuritis. In all three instances there was bilateral facial paralysis, paresthesia of the upper and lower extremities, and absence of tendon and periosteal reflexes. When such diffuse and generalized involvement does occur, it would appear that one is probably dealing with a meningoradiculitis rather than with a true peripheral neuritis. Fortunately the prognosis in such instances is good and, after a rather protracted period of convalescence, complete recovery usually occurs.

Optic neuritis occurring during the course of the disease or several days after all clinical evidence of parotitis has subsided has been reported by several individuals. Young[64] has reported a ten-year-old patient who thirteen days after bilateral parotitis complained of blurred and indistinct vision. Physical examination was essentially

negative except for drowsiness and an optic neuritis of four diopters. Four days later the patient became completely blind. Fortunately she regained her normal vision on the tenth day of her illness and made a complete recovery. In the case reported by Woodward,[65] the patient developed complete optic atrophy and blindness twenty-one days after parotitis. In both of the above instances there were clinical manifestations of meningeal involvement associated with the optic neuritis.

Personality changes, although rarely encountered, have been reported in the literature. Such changes are probably the result of a mild encephalitic process and usually do not manifest themselves until several weeks or months after the parotitis. The prognosis in these patients has been universally good, and none of the permanent sequelae that are so frequently seen following other encephalitic processes have occurred. Only one patient suffering from this type of disturbance has been seen at the Children's Hospital in Boston—a seven-year-old white girl who, two months after bilateral parotitis, became irritable, fussy, inattentive, and apathetic when alone. These symptoms persisted for six months during which time there was gradual improvement and finally complete recovery.

The treatment of mumps encephalitis is practically entirely symptomatic. Adequate caloric and fluid requirements should be maintained by the employment of appropriate measures, which of necessity must be determined for each patient. Proper elimination and care of the skin should receive constant attention. In those instances in which there is an increase in intracranial pressure, the intravenous injection of hypertonic glucose solutions or the administration of magnesium sulphate by mouth or by intramuscular injection will prove effective. Convalescent serum in amounts of 8 to 10 c.c. has been given in a few instances and has been thought by some to have been followed by improvement. As the natural course of the disease is one of improvement, it is difficult to evaluate properly any therapeutic procedure which might be of a specific nature.

Whooping Cough.—Complications involving the infections of the respiratory system have always received adequate attention, but little space has been allocated in the various textbooks to the neurologic complications of whooping cough. Yet these complications are not only just as serious as those involving the infections of the respiratory tract, but frequently produce irreparable damage—injuries that may completely impair the future mental development of the patient. It is not possible to determine the frequency with which these disturbances may occur. Friedlander,[66] Shaw,[67] and May[68] all state that such complications may occur in the course of the disease, but no definite statement as to the actual incidence of this disturbance is made. Ker[69]

states, "Convulsions very frequently are observed in whooping cough, and next to bronchopneumonia they are the most common cause of a fatal termination." He also adds, "They are, however, fortunately rare." The importance of this aspect of the disease is further stressed by the statement of Shamberg and Kolmer:[70] "Convulsions are always to be dreaded as they rank next to bronchopneumonia in relation to prognosis." From these remarks it at once becomes apparent that, although such sequelae are rare, yet they are of such importance that their consideration is justified.

When one realizes the ubiquitous distribution of this disease, and the fact that the majority of infants and children pass through its course without central nervous system manifestations, the lack of statistical evidence as to the exact *frequency* of neurologic complications is not difficult to understand. Toomey,[71] in a statistical review of over fifteen hundred cases of whooping cough, records five patients as having "spasmophilia" but does not state whether these convulsions were actually due to a lowered calcium in the blood serum (tetany).

The onset of these complications cannot be stated in terms of hours or days as the manifestations may appear either early or late in the course of the disease, or they may not become evident until several months after convalescence has occurred. This latter statement is particularly true in infants for in these patients it is often difficult to detect early mental aberrations. In the majority of instances in which convulsions mark the onset of pathologic changes in the central nervous system, the disease is usually in the third or fourth week of its course. In the sixteen patients who have been received at the Infants' and the Children's Hospitals of Boston on account of neurologic complications occurring either during the course of the disease, or on account of complications which manifested themselves after the disease had subsided, convulsions occurred in eleven patients. Of this group eight had convulsions during the third week of illness, one during the second, fourth and fifth weeks, respectively, and none during the first week. The fact that the majority of the patients who had convulsions suffered from them during the third week of their illness makes the speculation that the seizures might have been the result of minute hemorrhages instead of encephalitis interesting, for during this period of the disease the paroxysmal attacks of coughing are often at their height, and the opportunity for venous congestion of the intercerebral vessels with subsequent hemorrhage is not to be disregarded.

Convulsions occurring during the course of whooping cough have been noted since the earliest recognition of the disease and have always been considered as an unfavorable prognostic sign. Valentine[72] reviewed the records of eighty-three patients with pertussis, sixty-four

of whom had convulsions during their illness. Of these sixty-four patients, fourteen died; twenty-two developed spastic paralysis; and twenty-eight showed some residual neurologic disturbance. This was further emphasized in 1920 by Reiche.[73]

Until recently it was practically accepted as a universal truth that the convulsions were due to various degrees of intracranial hemorrhage, the severity of which was determined by the subsequent clinical course of the patient. Hockenbach[74] collected twenty-three cases in which a clinical diagnosis of brain hemorrhage had been made. In this group there had been nine postmortem examinations, which showed five cases with hemorrhage into the gray matter, two with hemorrhage into the cortex, and two with hemorrhage between the pons and dura. Schreiber[75] in 1899 reviewed thirty-eight cases with elven deaths. Autopsies performed in ten of the eleven cases showed minute hemorrhages in various parts of the brain which, however, the author felt were not sufficient to explain either the clinical course or the cause of death. In 1900 Hockinjos[76] studied forty-two cases in which a diagnosis of intracranial hemorrhage had been made from the clinical course of the disease. In a few cases postmortem examinations had been performed, and, although hemorrhages had been found, they were usually minute; he concluded that the evidence that the convulsions were due to hemorrhage per se was both insufficient and inadequate. Vidal,[77] Bloche,[78] Simonis,[79] Luce,[80] and West[81] have reported cases which at autopsy have shown not only minute hemorrhages in the brain, but also edema and cellular degeneration.

In 1904 Neurath[82] demonstrated early meningeal changes in fatal cases of whooping cough and offered the first data to disprove the previously accepted theory. In 1905 Rhein[83] reported a case of a twenty-one-month-old baby who, following whooping cough at three months of age, gradually became spastic, deteriorated mentally, had innumerable convulsions, and finally died. Autopsy examination showed regressive changes in the cortical cells and a diffuse proliferation of neuroglia. In 1919 Canelli[84] made postmortem examinations of two infants, six and twenty-three months of age, respectively, who died in coma during whooping cough, but no histologic lesions were found in either the vessels or the brain.

In 1924 Husler and Spatz[85] described typical regressive changes in the nerve cells of the cortex with not only loss of staining properties, but also of all structures of the cell except the nucleus. This observation added a new impetus to the study of whooping cough and is undoubtedly one of the greatest contributions to the satisfactory explanation of the neurologic conditions seen following this disease.

During the following year, these observations were confirmed by Jochims,[86] who suggested the term "whooping cough encephalopathy."

At the same time Neuberger[87] and Singer[88] described similar pathologic changes but thought that they were the result of air emboli, occurring secondary to a ruptured alveolus, following paroxysmal coughing, an observation which has not been confirmed. Berardi[89] and Sakanchi[90] in 1928 described changes similar to those observed by Husler and Spatz. Ford[91] has described the postmortem observations in two cases, both of which showed flattening of the convolutions, disappearance of sulci, edema, universal atrophy of cortical cells, proliferation of neuroglia, and slight dilatation of the ventricles. Askin and Zimmerman[92] recently reported the autopsy observations on a child dying from pertussis after four weeks of illness. The gross specimen showed a subarachnoid hemorrhage at the base of the brain, surrounding the left internal carotid artery, which was considered to be due to a torn pial vessel; microscopic sections showed diffusely scattered focal collections of small deeply staining mononuclear cells but without a true perivascular "collar" collection. Singer in 1929 reported six cases which showed a diffuse hemorrhagic encephalitis. In fact, he differentiates whooping cough encephalitis from epidemic, or toxic, encephalitis by the marked tendency toward diffuse microscopic hemorrhages.

Therefore, in view of the more recent work, it would appear that the time-honored theory of gross hemorrhage as the only cause of convulsions must be partially abandoned. Yet there is no doubt that gross hemorrhages may and do occur, as shown in a case discussed by Cabot[93] and in one of the cases included in this communication. However, realizing that convulsions are of prognostic importance, one should always exclude other etiologic factors which may precipitate these manifestations. I have special references to the work of Bluhdorn[94] and of Powers,[95] both of whom reported cases of whooping cough in which the convulsions were due to a low calcium in the blood serum, i.e., tetany, and readily subsided following proper therapy. An excellent review and discussion of the possible cause of convulsions occurring during the course of whooping cough has recently been published by Ellison.[96]

Mental retardation and *spastic paralysis* are so interrelated that it is probably best to discuss them together. However, the old assumption of gross hemorrhage as being the factor in every case must be partially replaced by encephalitis if we are to understand fully the underlying pathology resulting in mental retardation and spastic paralysis. There can be no doubt that gross hemorrhage per se may unquestionably produce such neurologic complications. Crothers[97] and Ford[98] have called attention to such conditions occurring in cases of intracranial hemorrhage following trauma at birth and in cases of hemorrhagic disease of the newborn. Ford has also shown at autopsy

definite cerebral atrophy following whooping cough, and by means of encephalography Crothers[99] has been able to demonstrate, during life, cerebral atrophy following intracranial hemorrhage, encephalitis, whooping cough, and other conditions.

Since the resulting pathologic changes in the brain are essentially the same both in whooping cough and in the other forms of encephalitis, the development of paralysis, be it flaccid or spastic, can be readily understood. Crothers has clearly shown by encephalography in whooping cough that the changes are due to widespread cerebral atrophy similar to those seen after an acute inflammatory or toxic process of the brain.

Myelitis occurring as a complication of whooping cough is rare. Mackey,[100] whose case simulates that reported by Moebius,[101] has described a case simulating Landry's paralysis with complete recovery. The former's patient was a three-year-old child who developed a typical ascending paralysis involving the lower extremities, upper extremities, diaphragm, and neck muscles. The author concludes that this is a peripheral neuritis similar to that seen in postdiphtheritic paralysis.

Visual disturbances, either temporary or permanent, are well-recognized complications. In 1928 Litvak[101] reviewed the literature concerning this phase of the disease and collected seventeen cases. Of this group two patients were permanently blind; thirteen had transitory blindness; and in two cases the ultimate results were unknown. Examination of the eyes showed the pupils to be reactive in seven cases, bilaterally dilated and nonreactive in ten cases; eight patients showed optic neuritis; one had choked disc; one had optic atrophy, one had ischemic fundi; and six had negative fundi. Two of his patients showed spastic paraplegia. The author attributed these disturbances to the following factors: (1) hemorrhage into the posterior limb of the internal capsule, (2) encephalitis, (3) multiple hemorrhages into the retina, and (4) toxicity.

During the past two years we have had under our observation two patients who have shown visual disturbances following whooping cough. In one case the disturbance was first noted when the patient was allowed out of bed, while in the second patient the condition had not been recognized until the time of her admission to the hospital.

In the majority of instances the *prognosis* in whooping cough encephalitis is not favorable. In fourteen of the sixteen cases studied in this report in which a diagnosis of encephalitis appeared justified, eleven of the patients have permanent injuries either in the form of mental retardation, paralysis, recurrent convulsions, or various combinations of these sequelae. Ellison, however, would apparently disagree with this opinion, for he states, "Protracted nervous disturbances fol-

lowing convulsions are the exception rather than the rule. (In 70 cases recently reviewed death occurred in 46 patients; 24 patients rapidly and completely recovered.)" Definite conclusions cannot be drawn from the small number of cases; yet such optimism in regard to sequelae as is expressed above is not universally encountered.

Brief case reports of some of the patients who have been treated at the Infants' and the Children's Hospitals of Boston are appended. In some instances, photographic copies of the encephalograms are included in order to demonstrate the widespread cerebral atrophy that may occur in this disease.

German measles (rubella) is usually considered as a rather benign contagious disease, of short duration, and without serious complications. However, during the past four months three patients suffering from central nervous system disturbances following in the course of the infection have been admitted to the Children's Hospital of Boston, and, in view of the fact that this disease has been quite prevalent during the past six to nine months, a consideration of this phase seems advisable.

Little information can be found in the literature regarding the *incidence* of complications of the central nervous system. However, one does note that the few cases which have been reported have occurred during an epidemic or when the disease has suddenly appeared among a large number of people in a small community. It is well recognized that the incidence of complications of any disease is usually increased when the disease occurs in an epidemic or endemic manner, and this may account for some of the complications and sequelae of rubella that are now appearing.

In 1921 Bénard[102] called attention to the occurrence of meningeal symptoms in thirteen patients during an epidemic of the disease, but since that time only an occasional case has been reported.[103-107] The case reported by Epstein[108] is of rather unusual interest as the patient's first complaints were inability to void and a progressive uncertainty of gait. This was followed by paralysis of the lower extremities and complete retention, thereby suggesting the development of transverse myelitis. Later, typical clinical symptoms of encephalitis supervened. The symptoms indicative of meningeal involvement have in the majority of instances appeared at a time when the rash was subsiding, although in some instances they have developed as late as the fifteenth or twentieth day. The manifestations have been as variable as the time of onset—some patients complaining of headache, diplopia, and vomiting, while others have developed convulsions or coma as the initial symptom. Examination of the cerebrospinal fluid has usually shown changes comparable to those encountered in other forms of encephalitis. Complete recovery has occurred in all

instances, although headache and sphincter disturbances have often persisted for several weeks after the other symptoms have subsided.

The three brief case reports that are included offer certain diagnostic problems although from the history, physical examination, and clinical course one seems justified in concluding that they represent central nervous system disturbances occurring as a complication of rubella.

CASE REPORTS

Morbilliform Measles

Case 1.—P. H., a white female child five years, three months old, was admitted to the hospital on account of unconsciousness of thirty-six hours' duration. The family and past history were irrelevant except that one sister had had measles two weeks previously. Six days before entry the patient developed symptoms suggestive of a respiratory infection, and forty-eight hours later a diffuse macular eruption appeared on the face and neck and rapidly involved the body surface. Thirty-six hours before admission, and at a period when the rash was fading, the patient became stuporous and complained of a headache. A few hours later she began to move her extremities in an awkward and purposeless manner, became delirious, and finally comatose. Physical examination revealed an acutely ill white child who could not be aroused when spoken to and whose arms and legs were in constant motion. Temperature was 102.4° F., respirations, 28; and pulse, 126 per minute. The entire body surface was covered by a fading copper-colored macular rash throughout which there were dispersed minute petechiae. The pupils were irregular in outline and varied in size independently of each other. The fundi were normal. The pharynx was deeply injected, and there was a profuse mucopurulent postnasal discharge. The neck showed resistance to anterior flexion. The sphincters were relaxed, and there was incontinence of both urine and feces. The remainder of the physical examination, including the reflexes, was negative. In view of the symptoms suggestive of a central nervous system disturbance, a lumbar puncture was performed and this yielded a clear fluid under 110 mm. of water pressure with a positive globulin, normal sugar reaction, and 56 cells, 86 per cent of which were of the lymphocytic series, the remainder being polymorphonuclear leucocytes. Bacteriologic examination of the fluid was negative. Further laboratory studies were of value in excluding other conditions. During the first few days of her hospitalization, the patient's condition remained essentially unchanged except for a gradual decline in temperature. On the fifth day the sensorium began to clear, and from that time she improved steadily. Twelve days after admission she was discharged with a residual slight right facial paralysis, and bilateral poorly sustained ankle clonus. A reexamination six months later failed to reveal any evidence of sequelae.

Case 2.—V. M., a white female child eight years of age, was admitted to the hospital on account of convulsions. The family and past history were irrelevant. Eight days prior to entry the patient developed coryza, photophobia, and conjunctivitis, and three days later a rash typical of measles appeared about her neck and face. Four days later, and at a time when the rash was fading, the patient assumed a rigid position, became unconscious, and had a generalized convulsion which was still present when she was received at the hospital (a period of eight hours). Physical examination revealed a normally developed, well-nourished, comatose female child, who was in a constant state of clonic convulsions. Temperature was 103° F.; pulse,

140; and respirations, 40 per minute. The body surface was covered by a fading copper-colored macular rash, which was more pronounced over the trunk and lower extremities than elsewhere. Except for a moderate injection of the pharynx, spasticity of the left lower extremity, flaccidity of the right lower extremity, and absent right patellar reflex, the remainder of the examination was essentially negative. In view of the evidence of meningeal disturbance, a lumbar puncture was performed which revealed a clear cerebrospinal fluid under 250 mm. of water pressure, with a positive globulin and normal sugar reaction and a total cell count of 54 cells, 51 of which were of the lymphocytic series. Bacteriologic studies of the fluid were negative. Forty-eight hours after entry the patient's facilities began to return, and by the fourth day she had become rational. At the time of her discharge from the hospital (fourteen days after entry), the patient had apparently made an uncomplicated recovery. Reexamination five months later failed to disclose any sequelae except a questionable degree of emotional instability.

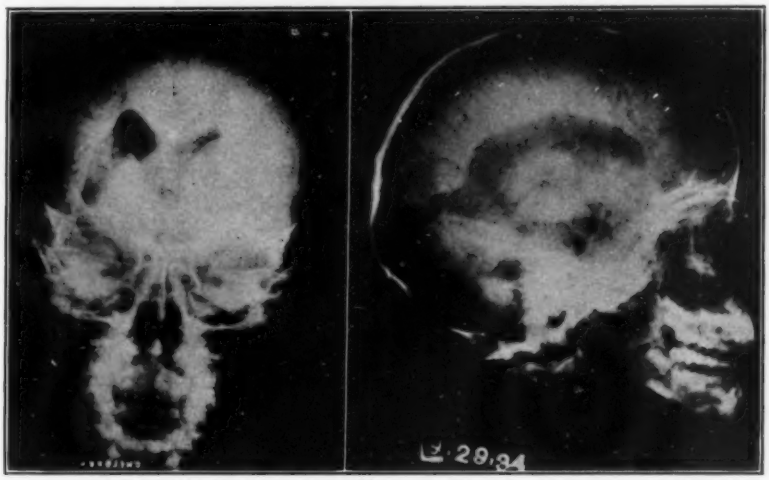

Fig. 1.—(Case 3) D. N., cerebral atrophy following measles encephalitis.

Case 3.—D. N., a white male child five and one-half years of age, was admitted to the hispital on account of mental retardation, and hemiplegia of the entire left side. The family and past history were irrelevant, and the patient had apparently developed in a normal manner until the age of two and one-half years, when he contracted measles which was accompanied by convulsions and stupor. On recovery it was observed that the boy had a left hemiplegia and appeared definitely mentally retarded. During the succeeding three years his condition had remained essentially unchanged. At the time of admission to the hospital the physical examination was essentially negative except for obvious mental retardation and left hemiplegia. Psychometric studies confirmed the impression of feeblemindedness and encephalographic studies (Fig. 1) revealed marked enlargement of both lateral ventricles (particularly the right ventricle) and also the third ventricle. There was also a moderate amount of air over the right hemisphere in the subarachnoid area but none over the left. The history, course, and examinations therefore suggested that the patient had a diffuse encephalitic reaction during the course of measles which had subsequently produced irreparable damage.

CASE 4.—R. B., a white female child four years and eight months of age, was admitted to the hospital on account of stupor and vomiting. Ten days prior to entry the patient developed measles and on the fourth day of her illness began to vomit, complained of a headache, and became stuporous. As her condition did not improve during the succeeding forty-eight hours, she was referred to the hospital. Physical examination revealed an acutely ill child who was quiet and stuporous when undisturbed, but very irritable and uncooperative when examined. Temperature, 101° F.; pulse, 116; respirations, 24; systolic blood pressure, 115; and diastolic, 75 mm. mercury. Further examination showed nuchal rigidity, hyperactive patellar reflexes, and bilateral Kernig signs. In view of these signs suggestive of meningeal irritation, a lumbar puncture was performed which revealed a clear fluid under normal pressure, with a positive globulin and sugar reaction, and three cells, all of which were of the lymphocytic series. Bacteriologic studies did not reveal the presence of organisms. Further laboratory procedures were of value in excluding other conditions. The patient remained in the hospital for a period of six weeks during which time there was a gradual disappearance of the meningeal symptoms; at the time of discharge she had apparently made an uncomplicated recovery. As the patient was not progressing satisfactorily at school, she returned to the hospital two years later when it was observed that she had developed typical postencephalitic facies, was emotionally unstable, unable to concentrate, and, by psychometric examination, not sufficiently competent to enter school.

CASE 5.—A. B., a white male child eleven years of age, was received at the hospital because of rapidly increasing drowsiness and stupor. Nine days before entry the patient had developed a rash typical of measles and was apparently making an uncomplicated recovery when on the eighth day of his illness he became drowsy and would sleep for unusually long periods of time. On the following day, this tendency became even more pronounced and was accompanied by inattentiveness and complete loss of interest in his surroundings. As his condition did not appear to be improving, he was admitted to the hospital. On examination the child did not appear to be disoriented but answered questions in a slow and halting manner, and, even when addressed, had an expressionless face. There was a fading copper-colored macular rash scattered over the trunk and lower extremities. Temperature was 99° F.; pulse, 80; and respirations, 20 per minute; systolic blood pressure 110 and diastolic 80 mm. of mercury. Except for slight muscular twitchings of the upper extremities and weak abdominal and cremasteric reflexes, the remainder of the examination was essentially negative. The cerebrospinal fluid was clear, was under 100 mm. of water pressure, and gave a positive reaction for both globulin and sugar. The total cell count of the spinal fluid was 26, and all of the cells were of the lymphocytic series. During the following forty-eight hours, the drowsiness became more pronounced, the patient finally becoming comatose. For the next fourteen days his condition remained essentially unchanged except that he had frequent tonic convulsive movements of the arms and legs. At the beginning of his third week of hospitalization there appeared slight improvement, which continued, and at the end of seven weeks he was discharged from the hospital definitely improved. Reexamination four months later showed that the child had apparently made a complete recovery.

CASE 6.—W. H., a white male child ten years of age, was received at the hospital on account of stupor and convulsions. Six days prior to entry the patient developed a typical measles rash and was apparently making an uncomplicated recovery, when, on the morning of admission he became inattentive and drowsy and suddenly had a generalized convulsion which lasted for from ten to fifteen minutes. Following this seizure he remained unconscious. Physical examination disclosed a normally de-

veloped and well-nourished white male child in a semicomatose state. Scattered over the trunk there was a faint and fading copper-colored rash. Temperature was 102° F.; pulse, 100; and respirations, 20 per minute; systolic blood pressure, 122; and diastolic, 90 mm. mercury. Further observations of interest were moderate nuchal rigidity, equivocal abdominal and cremasteric reflexes, and exaggerated ankle and knee jerks. Examination of the cerebrospinal fluid revealed a clear fluid under increased pressure with a positive globulin and sugar reaction and a total cell count of 800, about 90 per cent of which were of the lymphocytic series. Forty-eight hours after admission the patient began to regain consciousness, and on his sixth day of hospitalization was discharged. When he was seen five months later, the examination was entirely negative with the exception that he did seem to fatigue rather easily and was perhaps a little unstable emotionally.

Fig. 2.—(Case 7) Bilateral parotitis accompanied by encephalitis.

MUMPS

Group 1. Meningeal Manifestations Accompanied by Parotitis

CASE 7.—A white male child six years of age, was admitted to the hospital with the complaint of headache and stiff neck of twenty-four hours' duration. Ten days before entry the patient developed bilateral parotitis, which had persisted for three days and had been diagnosed as mumps. Twenty-four hours before entry he complained of a headache, vomited several times, and became drowsy. Physical examination revealed a normally developed and well-nourished boy, who did not appear acutely ill but who was drowsy when undisturbed and irritable when examined. Temperature was 101° F.; pulse, 100; respirations, 24; systolic blood pressure, 100; and diastolic, 44 mm. of mercury. Other observations of importance were stiff neck, hyperactive patellae, and a bilateral Kernig sign. The cerebrospinal fluid was under a pressure of 120 mm. of water, was ground-glass in appearance, gave a positive

chemical reaction for both globulin and sugar, and contained 1,700 cells per cubic millimeter, 94 per cent of which were lymphocytes. Bacteriologic examination of this fluid was negative, and other laboratory procedures yielded negative results. Ten days after admission he was discharged after having made an uneventful recovery.

CASE 8.—P. M., a white female infant one year and eight months old, was received at the hospital because of coma of six days' duration. Ten days prior to entry, or four days prior to the onset of drowsiness, she developed bilateral parotitis. On the fourth day of her illness, and coincident with the subsidence of the parotitis, she had a generalized convulsion which lasted for thirty minutes. During the next twenty-four hours she had two more severe convulsions and failed to regain consciousness following the last one. Six more convulsions occurred during the forty-eight hours prior to admission. Physical examination revealed an acutely ill and unconscious infant. Temperature was 99.4° F.; pulse, 100; respirations, 30. Other important observations were complete left hemiplegia involving the face, stiff neck, and a positive Kernig sign on the left but none on the right. The cerebrospinal fluid was under increased pressure, was clear, contained both globulin and sugar and 31 cells per cubic millimeter, 75 per cent of which were lymphocytes. Fourteen days after entry the patient was discharged with a persistent left hemiplegia, and, although she has received intensive muscle training and exercises, there is very little, if any, improvement.

CASE 9.—G. H., a white female child three years and seven months of age, entered the hospital on account of a stiff neck and vomiting of four days' duration. The family history revealed the fact that the patient's brother had had mumps three weeks previously. Physical examination revealed a moderately ill child who was stuporous when undisturbed but very fretful and irritable when examined. Temperature was 103.5° F.; pulse, 130; respirations, 40. The other important features were a stiff and retracted neck, hyperactive patellar reflexes, and a bilateral Kernig sign. The cerebrospinal fluid was under increased pressure, contained both globulin and albumin and 2,230 cells per cubic millimeter, 96 per cent of which were lymphocytes. Six days after admission, or ten days after the onset of symptoms, she developed typical bilateral parotitis. Twenty-one days after entry she was discharged after having made an uneventful recovery.

CASE 10.—T. R., a white male child five years old, was received at the hospital with the complaint of fever, vomiting, and headache of twenty-four hours' duration. The family and past histories were negative except for the fact that there were several cases of mumps in the neighborhood and that the patient had been intimately exposed to his brother who had had the disease three weeks previously. Physical examination revealed a child who appeared moderately ill with flushed face, bilateral submaxillary pain, stiff neck, hyperactive patellar reflexes, and a bilateral Kernig sign. Temperature was 102° F.; pulse, 130; respirations, 32. The cerebrospinal fluid was under a pressure of 250 mm. of water, was clear, contained both globulin and sugar, and 450 cells per cubic millimeter, 90 per cent of which were lymphocytes. Further laboratory studies furnished valuable information of a negative nature. Twenty-four hours later the patient developed typical bilateral parotitis, and five days later he was discharged after having made an uneventful recovery.

CASE 11.—J. G., a colored male child five and one-half years of age, entered the hospital on account of headache and vomiting of five days' duration. Nine days prior to the development of the headache, he contracted unilateral mumps, but, as he did not appear ill, he was permitted to continue his usual activities. Five days later,

when the parotitis was subsiding, he complained of a headache and began to vomit. As those symptoms persisted, he was subsequently brought to the hospital. Examination showed a well-nourished and normally developed boy who did not appear acutely ill. Temperature was 103.4° F.; pulse, 120; respirations, 34; systolic blood pressure, 104; and diastolic, 60 mm. mercury. Except for slight enlargement of the cervical glands there were no abnormalities noted. In view of the history and clinical course a diagnostic lumbar puncture was performed, and a clear cerebrospinal fluid under a pressure of 225 mm. of water was obtained. Examination of the fluid showed the presence of both globulin and sugar and a total cell count of 380 per cubic millimeter, 95 per cent of which were lymphocytes. Twenty-four hours after admission the temperature became normal, and the headache and vomiting stopped. Ten days after entry he was discharged.

Group 2. Meningeal Manifestations Not Accompanied by Parotitis

CASE 12.—J. M., a white male child three years and eight months of age, was admitted to the hospital on account of severe abdominal pain. Seven days before the development of this pain the patient had had a temperature of 103° F. and a severe sore throat, which had been diagnosed as acute follicular tonsillitis. This disturbance persisted for four days at the end of which time the boy had completely recovered. Thirty-six hours before entry he began to vomit, became drowsy, and complained of abdominal distress which gradually increased in severity. The family and past histories were negative except for the fact that *the patient's sister was recovering from mumps* and that he had been intimately exposed. Physical examination revealed a drowsy, stuporous, disoriented child with temperature 102° F.; pulse, 112; respirations, 24; and systolic blood pressure, 108; diastolic, 70 mm. mercury. The reflexes were not abnormal; but on account of the mental confusion, the vomiting, and the absence of satisfactory evidence to explain the course of events, a lumbar puncture was performed. The cerebrospinal fluid was not under increased pressure but was ground-glass in appearance, gave a positive globulin reaction, normal quantitative reduction test for sugar, and contained 1,300 cells per cubic millimeter, all of which were of the lymphocytic series. Bacteriologic smears and cultures were negative for organisms. By the fourth day after admission the temperature had become normal, and all clinical evidence of meningeal irritation had disappeared. During his period of hospitalization there was no visible involvement of parotid, submaxillary or sublingual glands.

CASE 13.—J. S., a white male child seven years of age, was admitted to the hospital on account of headache, fever, and vomiting of three days' duration. Twenty-four hours before entry he became irrational and semicomatose and had remained in this condition. Physical examination on admission showed an irrational, acutely ill child with a temperature of 102° F.; pulse, 100; respirations, 20. The observations of importance were inequality of pupils, right facial paralysis, stiff (but not retracted) neck, hyperactive patellar reflexes, a bilateral Kernig sign, and a tache cérébrale. A lumbar puncture performed soon after admission revealed clear cerebrospinal fluid under 550 mm. of water pressure, no globulin, a normal quantitative sugar, and 249 cells per cubic millimeter, 90 per cent of which were lymphocytes. Bacteriologic smears and cultures did not reveal the presence of any organisms. Further laboratory studies were of value in excluding other conditions. During the first twenty-four hours his temperature rose to 105° F., but this was followed by a slow defervescence, and by the fifth day his temperature had returned to normal. The meningeal signs began to subside seventy-two hours after entry, and at the time of discharge he had made a complete recovery.

CASE 14.—G. R., a white male child four years of age, was admitted to the hospital because of vomiting, headache and temperature of six days' duration. Six days prior to entry he complained of a severe headache and within a few hours began to vomit. For the following forty-eight hours there was no improvement. On the third day he had a generalized convulsion of four hours' duration. Examination at the time of admission was essentially negative except for drowsiness, stiff neck, hyperactive patellar reflexes, and a bilateral Kernig sign. Temperature was 101.6° F.; pulse, 120; respirations, 28; systolic blood pressure, 105; and diastolic, 70 mm. mercury. The cerebrospinal fluid was under increased pressure, was ground-glass in appearance, and contained both globulin and sugar and 500 cells per cubic millimeter, all of which were lymphocytes. Forty-eight hours after entry the temperature began to decline, and coincident with this there was a definite clinical improvement. There was a definite history of expocure to mumps, yet the patient did not present the usual clinical evidence of this disease.

CASE 15.—P. H., a white male child ten years of age, was received at the hospital on account of increasing drowsiness and abdominal pain of seven days' duration. For a period of one week the child had felt indisposed and preferred to remain in bed rather than play. During this time he had become drowsy, occasionally vomited, and complained of epigastric discomfort. The family and past histories were irrelevant. On examination he was quiet, apathetic, and obviously sick. Temperature was 99.6° F.; pulse, 84; respirations, 24; systolic blood pressure, 120; and diastolic, 75 mm. mercury. Except for nuchal rigidity, hyperactive patellar reflexes, and a bilateral Kernig sign, the remainder of the examination was negative. The cerebrospinal fluid was under 125 mm. water pressure, was clear in appearance, and gave a positive reaction for both globulin and sugar. Cytologic studies showed 225 cells per cubic millimeter, all of which were lymphocytes. The patient remained in the hospital for a period of twelve days and made an uneventful recovery.

WHOOPING COUGH

CASE 16.—E. B., a white female child four and one-half years old, was admitted to the hospital on account of convulsions. The family history was unimportant. When the patient was one year old, she had a severe attack of whooping cough, and during an attack of paroxysmal coughing she suddenly had a convulsion which lasted for several hours. Lumbar punctures performed at this time gave repeated blood-tinged fluid, which was thought to be due to intracranial hemorrhage rather than to trauma. These convulsive attacks occurred at frequent intervals for the following few days, during which time the patient developed an opisthotonic position with generalized muscular spasticity. This condition persisted for the following three months; during this period the patient received massage at regular intervals. At the end of a year she was able to move her right arm and leg but has never been able to move the left side. Prior to the onset of her illness the patient had been considered mentally normal, but since her illness she has obviously been mentally retarded.

Physical examination showed a fairly well-developed and well-nourished white female child, lying with her left arm and leg hyperextended and spastic. The right arm and leg showed slight spasticity but no deformities. She would notice neither objects nor sound, although she was not blind or deaf. The remainder of the examination was not important.

Air was injected into the ventricles by the spinal subarachnoid route. Roentgenograms showed enormously dilated but symmetrical ventricles (Fig. 3).

CASE 17.—J. B., a white male child seven years of age, was received at the hospital on account of retarded mental development. A review of the family and past histories was negative except for the definite knowledge that he had developed in a

normal manner until he was four years old, at which time he had whooping cough. Following this he appeared mentally retarded and was unable to progress in school. Repeated psychometric examinations showed marked mental retardation with no evidence of improvement. The encephalograms (Fig. 4) demonstrate the diffuse cerebral atrophy which followed this infection.

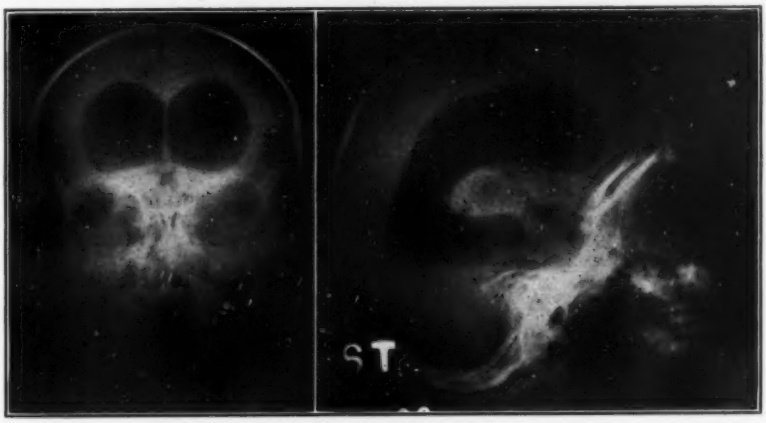

Fig. 3.—Whooping cough (Case 16).

Fig. 4.—Whooping cough (Case 17).

Case 18.—E. C., a white female patient eight years and one month old, was admitted to the Children's Hospital on account of repeated convulsive attacks of three months' duration. The past history was unimportant except that when she was five and one-half years old, she had an unusually severe attack of whooping cough. Three months prior to admission the patient dropped her fork while at the table,

and, when she reached to the floor to recover it, her right arm became rigid and spastic. This condition, however, lasted only a few minutes, and little attention was given to it. During the following month, she began to have frequent convulsive

Fig. 5.—Whooping cough (Case 18).

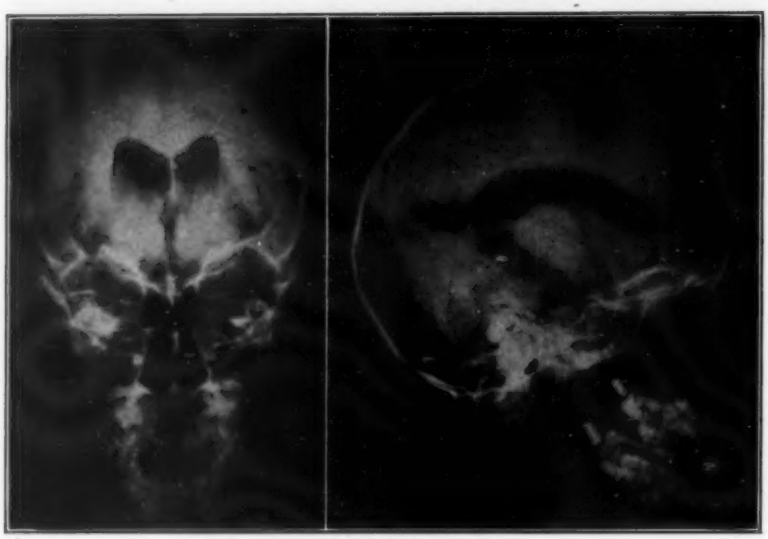

Fig. 6.—Whooping cough (Case 19).

attacks localized to this arm. One month before admission the patient began to have generalized convulsions, which, however, were always more pronounced on the right side.

Physical examination was essentially negative. Encephalograms showed normal ventricles, but there were two irregular lobulated calcified masses adjacent to each other just medial and slightly above the posterior portion of the left posterior horn, and a small calcified mass in the left inferior parietal region just inside the vault (Fig. 5). As no evidence of tuberculosis was present and as the configuration of the ventricles was not distorted, it was concluded that these masses were calcified hemorrhages—although we realize that we do not have irrefutable evidence.

CASE 19.—H. B., a white male child seven years of age, was admitted to the hospital on account of inability to walk, to talk, or to feed himself. The patient had developed in a normal manner until he was eight months old, when he contracted whooping cough and was critically ill; he remained in a semicomatose state and was not expected to live. Since that time there has been no evidence of subsequent mental development. The physical examination was negative except for the marked evidence of both physical and mental retardation. The encephalograms showed a marked enlargement and asymmetrical enlargement of the ventricles and an excessive amount of air subtentorially (Fig. 6).

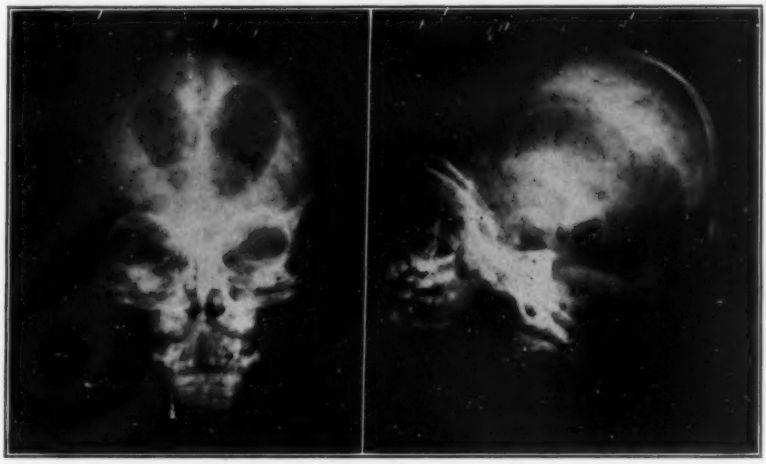

Fig. 7.—Whooping cough (Case 20).

CASE 20.—C. V., a white female patient nineteen months old, was admitted to the Children's Hospital on account of inability to move her left arm, left leg, and right arm. The family history was irrelevant. At the age of one month the patient contracted whooping cough from her brother, and during the course of the disease developed a bilateral internal strabismus, which has persisted throughout life. However, it was thought that she had made an uncomplicated recovery, and aside from the strabismus she had enjoyed good health until the present illness.

The present illness dates from one month prior to her admission, at which time she became drowsy, vomited several times, refused her food, and became unable to use her left arm, left leg, and right arm. About three days later the patient regained partial use of these members, but has not recognized her parents since the onset of the illness and has remained in a semistuporous condition.

Respirations were regular and even, and there was no cyanosis or muscular twitchings. Further examinations revealed bilateral internal strabismus, absent knee jerks, and partial flaccid paralysis of the left arm, left leg, and right arm. Dr. E. B. Dunphy's report of the eyegrounds is as follows: "Right eye shows a large area

of old choroiditis temporally to the disc involving macular region. The disc shows some haziness on nasal side; the vessels are about normal. Left eye shows sharply circumscribed patch of old choroiditis nasal to disc; the disc is definitely blurred, and the vessels are engorged. Cannot tell accurately about elevation. Child has a definite internal strabismus. This is probably dependent on the macular involvement of the right eye and dates back to the whooping cough, when the choroiditis probably occurred.'' Air was injected into the ventricles by the spinal subarachnoid route, and the roentgenograms revealed large dilated asymmetrical ventricles (Fig. 7).

CASE 21.—J. B., a white female child one year and four months old, was admitted to the hospital during the third week of whooping cough on account of recurrent convulsions and coma. Examination at that time presented an acutely ill, convulsive, and comatose infant with slight nuchal rigidity, hyperactive patellar reflexes, a bilateral Kernig sign, and poorly sustained bilateral ankle

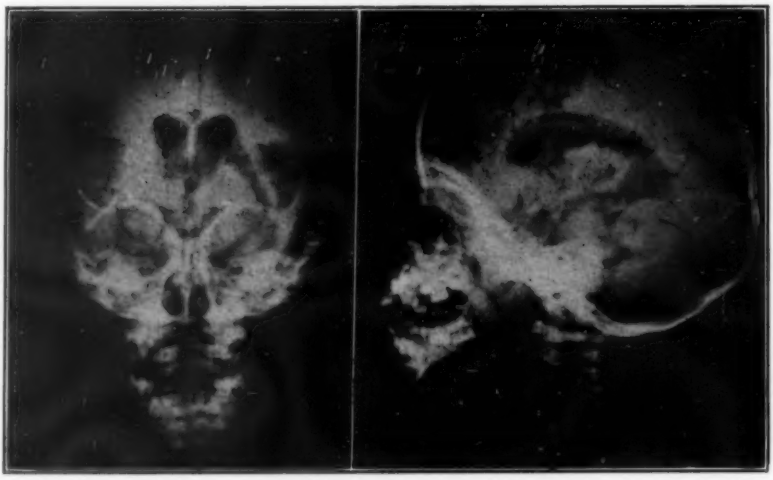

Fig. 8.—Whooping cough (Case 21).

clonus. A diagnostic lumbar puncture revealed a clear cerebrospinal fluid under slightly increased pressure, with a positive globulin and quantitative sugar reaction. Cytologic examination showed 8 cells, all of which were lymphocytes. Bacteriologic studies did not yield any further information. Tetany, though considered, was readily excluded. During the following few days the convulsions gradually decreased although the patient continued stuporous and would frequently cry out in a shrill ''meningeal cry.'' At the time of her discharge the infant presented definite evidence of mental retardation, and there was a mild quadriplegia. Since during the following two months her condition did not improve, she was readmitted to the hospital for further observation. Psychometric examinations showed that she was definitely deteriorating and the encephalograms revealed slight dilatation of the ventricles (Fig. 8).

Rubella

CASE 22.—J. B., a male child four years and nine months old, was admitted to the hospital on account of muscular tenderness and weakness of five weeks' dura-

tion. Six weeks prior to entry the patient and four other members of the family contracted German measles, from which all were thought to have made an uneventful recovery. One week after his illness the patient began to complain of generalized muscular tenderness, became apathetic, and developed a temperature of 102° F. These symptoms gradually became more pronounced and were accompanied by generalized muscular weakness and inability to sit erect or to walk. Physical examination revealed a normally developed and well-nourished white male child who, although irritable, did not appear acutely ill. Temperature was 100° F.; pulse, 120 per minute; respirations, 20 per minute; blood pressure, 120 mm. systolic and 90 diastolic. The examination was essentially negative except for palpable postauricular lymph nodes, generalized muscular tenderness and weakness, and absent patellar reflexes. Indicated diagnostic laboratory and roentgenologic studies were all of a negative nature with the exception of the cerebrospinal fluid examination which, however, revealed no abnormalities except for the presence of globulin (total protein 34 mg. per cent). During his period of hospitalization the patient gradually improved, and five weeks after entry was discharged. Subsequent reexaminations have shown a complete return of muscular function. The diagnosis in this incidence is problematical, and whether or not the peripheral neuritis appearing one week after convalescence was primarily due to German measles or some other focus of infection cannot be definitely stated. However, by the process of exclusion such a diagnosis seems tenable.

CASE 23.—D. H., a white female child nine years of age, was received at the hospital on account of a generalized convulsion. The family and past histories were irrelevant except for the fact that two weeks prior to admission the patient had German measles, from which she had apparently made an uneventful recovery. About four hours before admission, the child became unresponsive and did not seem fully aware of her surroundings; this apparent disorientation was soon followed by twitching movements of the facial muscles and finally by a generalized convulsion which was present at the time of entry. Physical examination was essentially negative except for temperature of 102° F., pulse of 110 per minute, respirations of 20 per minute, blood pressure of 156 mm. mercury systolic and 70 mm. diastolic, absent patellar reflexes, and generalized convulsive movements which were more pronounced on the right than on the left side of the body. Diagnostic laboratory and roentgenologic studies were negative, with the exception of the spinal fluid which was under increased pressure (325 mm. water), was slightly opalescent, yielded a positive qualitative test for globulin and sugar, and contained 90 cells per cubic millimeter, 88 per cent of which were of the lymphocytic series. One hour after entry, and following the administration of sedatives, the convulsion ceased, and the patient became rational. During the succeeding few days she complained of severe headache and became unable to retain anything given by mouth. Reexamination at this time showed bilateral papilledema and an exaggeration of the deep reflexes. The symptoms of increased intracranial pressure were relieved by injections of hypertonic glucose solutions intravenously and magnesium sulphate intramuscularly. Coincident with her clinical improvement and with the subsidence of increased intracranial pressure, the cerebrospinal fluid assumed its normal properties. Reexamination of the patient one month after discharge failed to reveal any sequelae.

CASE 24.—G. M., a white female child three years of age, was admitted to the hospital on account of ataxia and nystagmus of forty-eight hours' duration. Eight days prior to the onset of the symptoms the child, along with three others in the family, developed German measles, but was only slightly indisposed and after three days apparently recovered. On the fifth day after the rash had dis-

appeared, it was observed that the child fell when she attempted to walk, that she was very unsteady, and that her eyes "rolled." As the condition did not improve, she was brought to the hospital. On examination the patient appeared well nourished and developed and not acutely ill. Temperature was 99° F.; pulse, 120 per minute; respirations, 20 per minute; and blood pressure, 95 mm. mercury systolic and 70 mm. diastolic. Except for a bilateral five vertical and lateral nystagmus, coarse tremors of the hands and head, ataxia and hyperactive patellar reflexes, the examination was negative. Indicated roentgenologic and laboratory studies including the cerebrospinal fluid examinations were negative. Five days after admission the physical signs had completely disappeared, and the patient was discharged. At the time of her discharge it was difficult to decide whether she had had a toxic labyrinthitis or encephalitis as a complication of rubella. One month after leaving the hospital she was readmitted on account of drowsiness and irritability. A few hours later she had a generalized convulsion which was followed by coma of several hours' duration. On regaining consciousness, the child rapidly improved but within the course of a few days presented very definite personality changes. In view of the course of events it now appears that the patient's original illness was of an encephalitic nature rather than a toxic labyrinthitis.

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FIFTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

Round Table Discussion on Poliomyelitis

NEW YORK CITY, JUNE 7, 1935
WALDORF-ASTORIA HOTEL

Leader: Dr. John A. Toomey, Cleveland.

Assistants: Dr. Carl H. Laws, Brooklyn, and Dr. Pascal F. Lucchesi, Philadelphia.

The meeting was called to order at two-thirty o'clock, at the Waldorf-Astoria Hotel, Dr. John A. Toomey, of Cleveland, presiding.

CHAIRMAN TOOMEY.—There are three subjects to be considered in this conference on poliomyelitis—the rôle of convalescent serum, the mechanism of the production of the disease in the human, and poliomyelitis vaccine.

I. Dr. Laws introduced the topic, "The Use of Convalescent Serum in the Prevention and Treatment of Poliomyelitis; A Critical Evaluation of the Literature."

DR. CARL H. LAWS (BROOKLYN).—In Landon's series[1] of 597 preparalytic cases, 118 received convalescent serum; 73 received horse serum; and 396 received no treatment. No striking difference in the results of these three groups was noted so far as the development of subsequent paralysis is concerned. The mortality was about twice as high in patients treated with convalescent serum and nearly three times as high in patients receiving horse serum as in the patients receiving no serum therapy. A consideration of the day of illness on which serum was administered shows that serum therapy was administered in the majority of cases early in the disease. No conclusions can be drawn from a consideration of the day of illness on which paralysis developed.

Harmon[2] compiled the experiences of numerous investigators who have treated acute epidemic poliomyelitis with various types of serums, in all 4,400 treated cases as compared with 2,660 untreated cases, the two series occurring coincidentally. Of the treated patients, 2,637 were seen early in the disease, the majority being in the preparalytic stage.

The uncertainty of the course of the earliest type of poliomyelitis, the preparalytic stage, has been responsible for the apparently brilliant results when treatment has been applied in this stage. The outcome in patients treated in the preparalytic stage does not differ from the average for untreated patients. Recent therapeutic experiments in which convalescent serum was given to alternate patients by Kramer and his associates and by Park support the same contention, showing no difference in the average outcome in treated and untreated patients.

Notwithstanding the total failure of statistical presentations to favor certain types of serums, clinical observations almost universally made of rapid symptomatic response to the administration of serum by an immediate drop in temperature and marked improvement in symptoms cannot be totally disregarded. All other forms of therapy in this disease have been a signal failure, with the possible exception of spinal drainage. There appears to be enough evidence from clinical observation to warrant the continued use of serums in early stages of acute poliomyelitis.

Fischer[3] analyzed data collected for the purpose of determining the value of convalescent serum in the treatment of preparalytic poliomyelitis. He showed that the sex, age, stage of the epidemic, day of treatment, dosage, and method of administration of serum had no influence on the outcome of the disease so far as could be determined statistically, while, on the other hand, the temperature, cell count, and general clinical impression could at times be used as an indication of the degree of severity of the illness.

Our present study has demonstrated that there is no proof that a physician is depriving his patient of an equal chance for complete recovery by not administering convalescent serum.

Park[4] states that statistically there is no evidence that the serum did any good; also, as stated by Kramer and Aycock, there is no evidence that it did any serious harm.

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DR. S. D. KRAMER (BROOKLYN).—Should you use convalescent serum or not? The answer is yes. We began to use convalescent serum because it neutralized the virus. However, recent experimental evidence has indicated that the virus reaches the central nervous system long before the disease is recognizable and that the virus is fixed early in the tissues. It is difficult to understand how the serum could do very much, although possibly it might make the disease milder. It might prevent more virus from reaching the central nervous system. On the other hand, our failures may be due to the fact that we have not tried a very potent serum. Why limit the administration of serum to 50 c.c. or 100 c.c.? Why not 400 c.c. or 500 c.c.? In short, we should try the quantitative effect of serum. We have found beneficial effects in cases in which we have used as much as 400 or 500 c.c., given in six- or eight-hour intervals, 10 c.c. at a time.

DR. P. M. STIMSON (NEW YORK CITY).—The three authors whom Dr. Laws quoted all used very much the same material and got approximate results. At the Willard Parker Hospital we feel that the one essential thing in the treatment of poliomyelitis when diagnosed in the preparalytic stage is rest and quiet, even if necessary to obtain it with narcotics. Don't tamper with the central nervous system and keep the patient absolutely quiet.

DR. M. B. GORDON (BROOKLYN).—As Chairman for the Brooklyn Division of the Commissioners' report, and also for the County Society, I had occasion to include in our statistics all the private hospitals of Brooklyn in 1931. Our results were the same as those reported by Dr. Landon and Dr. Fischer for the entire city.

Transfusions from immune donors were tried with about the same results.

At the Kingston Avenue Hospital we rest the patient and make frequent spinal taps.

DR. EDWARD MARTMER (DETROIT).—Do you mean repeated taps or sample taps for diagnostic purposes? It has been my feeling that many of these patients are not benefited by repeated spinal drainages.

Wouldn't we be better off if we took the opposite attitude and attempted dehydration of the cord by the hypertonic solutions intravenously?

DR. GORDON.—The method used at the Kingston Avenue Hospital during the past few years, is to have one diagnostic tap. We do not repeat the taps. We have not used hypertonic solutions.

CHAIRMAN TOOMEY.—I would agree with Dr. Stimson that these patients should be left alone, merely puncturing them for diagnosis. In cases of bulbar involvement we even hesitate to puncture.

DR. KRAMER.—Why do you hesitate?

CHAIRMAN TOOMEY.—Because of several unfortunate experiences that followed lumbar puncture in this type of case.

DR. KRAMER.—I know that these patients cannot stand any intraspinous therapy, particularly in the bulbar type of case.

CHAIRMAN TOOMEY.—Occasionally, children who have a spinal type of disease may have a headache that you can relieve with a lumbar puncture. Isn't that your experience?

DR. STIMSON.—Yes. If there is a high cell count, I think sometimes it is well to take of a little more of the fluid—I mean a count of 1,500 with meningeal symptoms.

DR. LAWS.—In the epidemic of 1931, the consulting physicians immediately made a tap at the bedside after a complete examination of the child and started to inject the serum intraspinously at that time. This produced a rise in temperature with associated neck rigidity and meningeal symptoms. Because of these reactions, they gave their subsequent injections of serum intravenously.

II. Dr. John A. Toomey introduced the topic, "Mechanism of the Disease Production in the Human Being."

DR. TOOMEY.—There are two theories. The first is that the virus enters by way of the olfactory terminal fibers and spreads along the olfactory nerves to the bulb, thence to the hypothalamus, to the medulla, thalamus, and midbrain, down the spinothalamic tract to the posterior column, finally reaching the anterior horn cells of the lumbar or other parts of the cord. The second theory is that the disease reaches the cord by way of the gastrointestinal tract. I think that the second theory is more logical from a clinical standpoint.

The pathologic and clinical end-results are the same both in the human being and the *Macacus rhesus* monkey no matter what the portal of entry, but I think that the mechanism whereby the pathologic condition is produced is totally different in each of these species. I will try to limit myself to the mechanism of spread in the human being.

Poliomyelitis virus could be considered to have an almost obligate affinity for gray fibers anywhere in the body.[1] Its absorption depends upon its ability to contact the axis cylinders of nerve fibers in a natural or unnatural way. Whether this virus that has been absorbed by the axis cylinder will reach the central nervous system and cause damage depends upon the size of the absorbing nerve, its nearness to the central nervous system, whether its axis cylinders are medullated, and upon the amount absorbed by the latter.

There is direct connection between the sympathetic fibers of the intestine and the cord. Some fibers, especially the vasomotor, run directly to the intermediate zone in the cord just posterior to the anterior horn cells.[2] A poison absorbed along this pathway would probably destroy contiguous structures, i.e., the anterior horn cells. Because most paralyses occur in the lower extremities, the probabilities are that absorption would take place from a site in the intestine, the nerves of which are derived from the same segments, i.e., those in the lower ileum and cecum. Should this be true, we have a definite anatomic method of spread of the poison and an explanation that fits the clinical facts (Fig. 1). There is irritation of reflexes as the virus reaches the somatic part of the nerve via the sympathetic fibers, pain as

it passes over the sensory nuclei of the ganglion cells, loss of reflexes and destruction of anterior horn cells when the virus spreads to and involves contiguous structures. Since the virus has an affinity for gray fibered unmedullated nerves and travels poorly, if at all, along medullated ones, unless they have been irritated, then the areas where spreads would most likely occur along the sympathetic chain would be in those places where there are no white rami communicantes and no medullated nerves, i.e., between lumbar I and sacral II in the lumbar enlargement and above thoracic I in the cervical enlargement. The muscles that are supplied by nerves from the segment lacking white rami communicantes should be the most commonly involved, and this is what we find clinically.

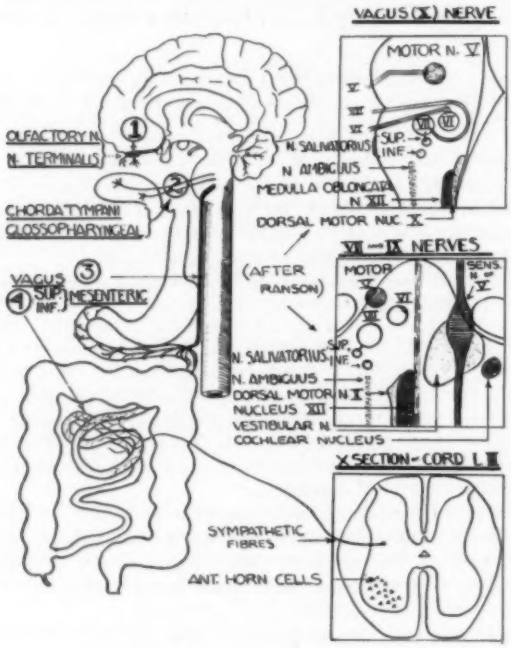

Fig. 1.—Poliomyelitis virus pathways.

But you may say that virus is never found in the stools of patients with poliomyelitis! If the virus has an affinity for gray fibers and becomes fixed to these after absorption and the process of healing occurs only as in any other inflammation with absorption from the spot of localization, then it would be surprising indeed if we ever found virus present in the stools of the human being during the first stage of the illness. Paralysis does not result immediately after absorption, and days may elapse before symptoms occur, during which time the intestines will have been cleared of remaining virus; thus when paralysis becomes obvious, it cannot be found free in the intestinal contents. This explanation has been enlarged elsewhere.[3]

But monkeys fed with the virus never get the disease! This does not rule out the gastrointestinal portal of entry. First, the monkey is not naturally a susceptible

animal, and second, all such experiments were not planned to have the virus approximate the gray-fibered axis cylinders of the gastrointestinal tract. When this was done, the disease was easily produced experimentally.[4]

How do these patients get bulbar palsies? The pictures of true bulbar palsy and the bulbar palsy seen in poliomyelitis are not exactly the same. The latter first shows involvement of the muscles supplied by both nuclei ambigui of the vagus. The later clinical picture is due to local extension. Absorption by the vagi from the gastrointestinal tract and extension to the bulb would give the picture we see in poliomyelitis.[5] But you may say, Why isn't the vagus involved in every instance? The lower motor neurones of the vagus are a ganglionated, gray-fibered set of plexuses in the wall of the intestines, which easily absorb the virus. These neurones end in the intestine in synaptic connection with the medullated connector fibers of the vagus. A synapsis and a medullated nerve tend to stop the spread. Nevertheless, the virus may be strong enough to bridge the synaptic gap and cause the so-called bulbar paralysis when the poison reaches the nuclei ambigui of the bulb. This condition has been produced experimentally.[6] The local glandular enlargements in the mesentery are easily explained as being the result of local stasis in a paralyzed gut with some local inflammatory absorption. We do not need to have a general infection to explain this condition.

In every epidemic of poliomyelitis there will be found cases with only isolated involvements of the seventh nerve. We cannot explain these cases on the basis of absorption from the lower part of the gastrointestinal tract, but we can if absorption takes place from the upper portion of the alimentary tract, i.e., from the taste buds of the tongue.[7] The taste buds have connection with the nucleus salivatorius, and simple extension to the adjacent seventh nerve from the latter could produce isolated nuclear paralyses. This condition likewise has been produced experimentally.[8] The tractus solitarius is not shown in Fig. 1.

The agglutinins for the enteric group of organisms are decreased;[9] the stools of poliomyelitis patients are more toxic;[10] and the blood picture is significant. Autonomic drugs show a sympathetic localization,[11] and the autonomic fibers of the gastrointestinal tract and bladder are often involved before the somatic fibers.[12]

DR. KRAMER.—I noted that, although you tried to limit yourself, you nevertheless had to refer to the experimental disease in the monkey. After all, there is no disease that can be produced in the exact counterpart as poliomyelitis in the experimental animal. True, it is not a disease native to the monkey, but, once the virus is established in the monkey strain, the animal becomes decidedly susceptible to it. It is a different story when we take the human strain and try to establish it in the monkey; we get a queer disease. It doesn't prostrate, or hardly paralyzes, until it has gone through a number of passages. We then can infect by putting a drop of the virus into the nose; yet it is extraordinarily difficult to infect them by the gastrointestinal route unless we do an unusual procedure, i.e., give large doses of morphine and large doses of virus to eat.

Your diagram is very instructive for it pictures how the disease may be haphazard, but there are other things to consider. Epidemiologically, poliomyelitis is a contact disease, as much a contact disease as measles, diphtheria, whooping cough, and scarlet fever. Our mode of infecting the experimental animal falls right in that category of upper respiratory infections. We readily infect the monkey by introducing the virus into the nose. Furthermore, both in the human being, as well as the experimental animal, we may find the virus in the nasal mucous membrane; and it has been found a number of times in the nasal secretions—all of it indicating an oral and nasal introduction. No matter how we infect a monkey, as soon as it contracts the disease, we can regularly get the virus from the nose and throat, thus pointing toward a nasal introduction, a nasal route of infection.

Certainly, Fig. 1 helps to explain the haphazard distribution of paralyses.

DR. STIMSON.—You said that the cranial paralysis was central and not peripheral. You mean that it attacks the nucleus rather than the nerve fiber itself?

CHAIRMAN TOOMEY.—I think it is absorbed by the vagus nerves bilaterally first and then later attacks the nucleus. There is too much stress laid upon epidemiology. How many other diseases in the history of medicine were contact diseases before it was found out exactly how they were brought about? You could explain the epidemiology of this disease just as well by stating that it is caused by some common poison which enters by way of the gastrointestinal tract or with things that people eat and drink. I do not think that the printed evidence shows clearly that this disease is actually a contact one. No interne or nurse ever got poliomyelitis on my service, nor have I ever heard of anyone working with the virus who has contracted the disease. I have had instances of two or more cases in one family,

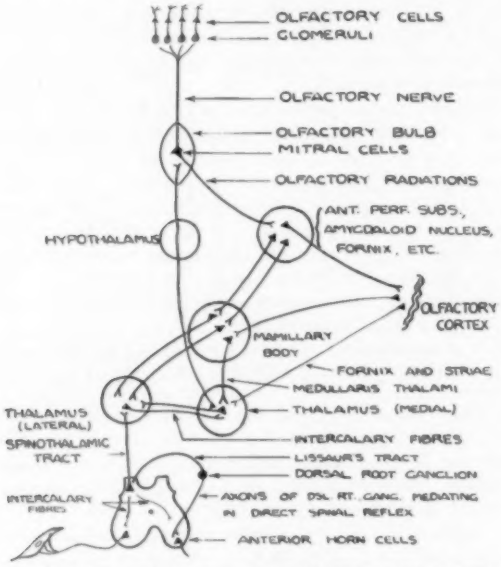

Fig. 2.—Poliomyelitis virus via olfactory portal of entry.

but, when I analyzed the occurrence of the disease, I usually found that their symptoms started approximately at the same time, only in one the disease progressed at a faster rate than in the other.

Dr. Kramer does not disprove my facts but counters by saying that there are better reasons for thinking that the virus enters elsewhere. His remarks make it necessary for me to refer to the theory of spread via the olfactory area. He states that the evidence favors the idea that the portal of entry is through the nasal mucosa. Does the anatomic evidence favor such a contention? Let us examine Fig. 2 which in schematic form tends to depict how the virus spreads according to the olfactory theory of spread.

The virus is said to be absorbed by the olfactory fibers, and finally after traveling all over the nervous system it reaches the motor cells in the lumbar area. During these lengthy travels of the virus, it usually gives no clinical evidence of its presence until it reaches the lumbar area.

It is claimed that the virus has a special affinity for motor cells in the lumbar area, or that these cells have a decreased susceptibility to this poison. If this is so, how about the motor cells of the bulb, or those of the cervical area that in some cases become involved after the cells of the lumbar area. In these instances, we would have the virus traveling down through the nervous system to reach the lumbar enlargement and then trekking back up the cord again to involve the cervical and bulbar areas. It appears to me that, if the olfactory area was the portal of entry, the cranial motor nuclei should always be involved first.

The fact that you can give a monkey poliomyelitis with the greatest of ease by way of the olfactory area does not allow you to conclude that this is the portal of entry. You merely demonstrate the admitted fact that, where the nerve connection with the central nervous system is short, the production of the disease will be more probable with a smaller amount of virus than it will be by another route.

No one who holds that the virus is absorbed in the olfactory area has given a logical reason why in the monkey the virus doesn't give any clinical symptom of its presence until it gets down to the lumbar or cervical area.

DR. KRAMER.—There are a number of features that speak against the gastrointestinal route. Dosage may be one of them. Of course, we know very little about the amount of virus necessary to infect. The virus doesn't grow anywhere except in the animal body. The amount of virus probably picked up would be rather small. This would seem to argue against absorption via the gastrointestinal tract. We cannot explain the haphazard appearance of paralysis in this disease, but I think we err when we emphasize the fact that no paralysis commonly occurs until the virus reaches the lumbar region. I think perhaps that one of the reasons we see a little more paralysis of the lower extremities than of the upper in monkeys is that they use the legs to stand on, and we notice it more. We do not notice the arms quite as readily as the legs, but there may be involvement of the arms without involvement of the legs in monkeys.

CHAIRMAN TOOMEY.—Of course, monkeys and human beings may have paralyses of the muscles of the arms only, but that was not the point. The question was, How does it happen that the lumbar area is involved first and the cervical only secondarily in the average case in which there is such a combination involved?

Much has been said about the experimental disease in monkeys. You inject monkeys intracerebrally or by nasal instillation, and the disease is produced, nearly 100 per cent of the animals developing quadriplegia and dying. Is that the exact counterpart of the picture seen in the human being? No, for there we have isolated muscle palsies, bulbar palsies, etc. Don't you think you should have as your objective the production of the same clinical picture in the experimental animal?

My conception as to why the virus first involves the lumbar enlargement in the experimental animal no matter where the virus is introduced is simple. The virus passes down the cord and out over the sympathetic ramifications to the gastrointestinal tract, and the gut becomes paralyzed. Toxins are now produced in the stased areas of the gut; then these toxins are absorbed back over the saturated sympathetic system; and finally paralysis is produced in the animal when these toxins reach the anterior horn cell. If it is admitted that in monkey cord virus we have only one of the isolated factors necessary to produce the disease, relatively innocuous in itself and that the secondary factor is produced in the gastrointestinal tract of the animal by its own resident organisms, then we can easily explain the vagaries of the disease.

In the human being, however, the poison that causes poliomyelitis is delivered "tailor-made." In the monkey you inject one factor, and it produces the other in its own economy. If you take baby monkeys and inject them with massive doses of

enteric toxins and vaccines to the point where they are saturated and then inject them with virus, you get immediate hemiparesis.[13] If you take enteric toxins and inject them intracerebrally in the monkey, you find no paralysis. But if you take minute quantities of toxin plus virus, you get immediate hemiparesis.[14] In the human being, you would have the paralysis of any motor horn cell that contacted this "tailor-made" combination, and absorption from the spots I have diagramed are entirely logical.

If you take the blood serum of human beings with poliomyelitis at the height of the disease, you will find that the agglutinin titer against enteric organisms is lower comparatively than it is when they get better.[9] If you examine the blood serum of any monkey which dies from the disease at the stage of prostration, you will find its enteric agglutinins titer is practically nil.[9] When older monkeys which have some agglutinins are vaccinated with small amounts of enteric toxin and vaccine and injected with virus intracerebrally, the result is a prolongation of the incubation period.[15] If in monkeys you inject the superior and inferior mesentery ramifications of the gastrointestinal tract to the point where you get paralysis of the gut, then leave them alone until the agglutinin titer against the enteric organisms is practically nil (about ten days), and then inject them with virus intracerebrally, you get immediate hemiparesis.[16]

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DR. E. CUSHING-LIPPITT (MILWAUKEE).—In 1919 there was a small epidemic of poliomyelitis in Milwaukee, the majority of cases having been reported late in July, August, and early September. In practically all cases that I saw and reported upon, gastrointestinal symptoms were the earliest ones noted by the mothers of the children; only a few reported upper respiratory symptoms as well.

In many families, several children would be ill, but possibly only one would develop paralysis. We were rather inclined to the idea after seeing a number of these patients that the other children who had gastrointestinal symptoms had abortive cases of poliomyelitis.

CHAIRMAN TOOMEY.—There is one point that comes to me that I think clinches this thing from a clinician's standpoint. Every one of you who has cared for cases of this disease has seen patients come into the hospital with paralyzed

intestines and urinary bladders. They have had paralysis so complete that the mothers will tell you that enemas given were not returned and that these symptoms occurred long before the children ever got any somatic paralysis. How can anyone explain these facts on the basis of olfactory absorption? You must admit that such patients have autonomic involvements.

Long before these children will have somatic paralysis, they will have paralysis of the sympathetic system, paralysis of the gut. They will have urinary bladder paralysis in severe cases and yet not have muscles involved whose nerves come from the very same segment. No explanation will satisfy these clinical facts save the one that admits that the sympathetics are involved.

DR. KRAMER.—That is rather an uncommon occurrence.

CHAIRMAN TOOMEY.—Not in our experience. The important thing to think about is not that the bladder is paralyzed, but the fact that the paralysis of the bladder occurs before you get any somatic paralysis and that even when somatic paralysis occurs, it is usually unassociated with paralyses of muscles supplied by somatic nerves from the same segmental area.

DR. KRAMER.—Why doesn't it occur more often?

CHAIRMAN TOOMEY.—Pain was mentioned. You can easily explain the pain as being due to irritation as the virus combination passes the ganglia on the way to the cord.

DR. KRAMER.—The pathology of the disease explains the pain quite adequately. We find there is a diffuse infiltration around the ganglia.

CHAIRMAN TOOMEY.—There is some trouble around the posterior horn, but no marked disturbance in discrimination nor temperature dissociation. All you have is pain.

Was not there a point made about the gastrointestinal tract that I did not answer?

DR. KRAMER.—I asked that if the gastrointestinal tract is involved, why we don't get more symptomatology referable to the source.

CHAIRMAN TOOMEY.—Isolated loop paralyses for a few segments will not give many obvious objective signs. It is only when the intestinal paralysis is massive that we begin to note this fact.

DR. GORDON.—Did I understand Dr. Kramer to say that the bladder symptom was infrequent? I thought it was common.

CHAIRMAN TOOMEY.—I feel it is a very common symptom also, often missed, because the physician is satisfied if the patient is urinating. He does not realize that the bladder is full and that the patient has paradoxical retention with dribbling; he does not urinate; he just dribbles when the bladder becomes overdistended. These patients must have paralysis of the detrusor muscle and the sphincter as well, one supplied by the parasympathetic and the other by the sympathetic nerves.[12] However, the sacral muscles are normal. The patient can wriggle his toes, the center of origin seems normal; but yet he cannot urinate. The lesion, therefore, must be peripheral.

DR. MARTMER.—Did you say you believe this is not a contact disease?

CHAIRMAN TOOMEY.—Yes, even though the evidence often seems strikingly in favor of its being a contact disease.

DR. MARTMER.—We have situated about 200 miles north of Detroit a camp which accommodates about 150 boys from eight to sixteen years and which is

practically isolated. For the first six weeks, there were no difficulties at all. Contrary to the rules and regulations, at the end of this six-week period, they admitted one boy who had been in California with his sister and who had come to Detroit. On the way from California he had had a gastrointestinal upset. A few days after he was in the city and after he had left for camp, his sister developed frank poliomyelitis.

This boy was taken into a cabin with seven other boys at the camp. We could not find any records of poliomyelitis north of Bay City, Mich., up to that time. Within seven days after he was admitted to the camp, three boys in that particular cabin contracted poliomyelitis, as well as two other boys who had been thrown into contact with that group. Half of the other boys of the camp were away on an expedition about five days, carrying food from camp and not buying anything on the way; there was no poliomyelitis in that group at all. There was no poliomyelitis anywhere else in the camp except in the cabin where this boy was and in the cabin adjoining.

To clean the thing up, the camp was broken at the end of a week; the only secondary cases that arose in the groups (and they were each one traced very carefully when they returned to the city) were in boys who had been in more or less contact with that first particular cabin, and in one instance with the second cabin where the two secondary cases occurred.

I grant you that this is not positive proof that it is either an epidemic disease or one spread by contact, but it is as close to a perfect experiment as you can get under such conditions.

CHAIRMAN TOOMEY.—I grant all of the facts, and yet I wonder if we couldn't explain them in another way. Personally, I think that the gastrointestinal droppings may be infectious, and yet the disease not be classed as contagious. Was the food and milk supply the same for all?

DR. MARTMER.—Some of the others had exactly the same food supply.

CHAIRMAN TOOMEY.—Dr. Martmer makes a good case. On the other hand, if you insist on this being a contact disease, how can you explain those cases that occur out in the country, isolated from everybody else, cases that have had no possible exposure?

III. Dr. Lucchesi introduced the next point, "The Use of Vaccine in the Prevention of Poliomyelitis."

DR. LUCCHESI (PHILADELPHIA).—Kolmer and Brodie, working independently, have recently developed vaccines which they believe can be safely used to immunize many against poliomyelitis. The use of vaccine in the prevention of this disease in monkeys is not new, but it is in its application to man. The virus of poliomyelitis has been used as a preventive measure experimentally in monkeys (1) as dead virus, (2) as a living virus, and (3) as an attenuated virus. Flexner and Lewis[1] and others in 1910 used a virus killed by heat to immunize monkeys but were unsuccessful. However, they were successful in later experiments by the subcutaneous injection of graduated doses of living unattenuated virus. But this method was not practicable, as it occasionally produced poliomyelitis in the monkey. Because of this fact, research workers felt the necessity for producing immunity by the use of attenuated virus. Such attenuation was accomplished by heating, drying and the use of chemical agents as phenol, formaldehyde, sodium ricinoleate, and aluminum hydroxide. Various routes of inoculation were suggested to demonstrate the ability of the virus to vaccinate the monkey against poliomyelitis. It was given intradermally, subcutaneously, and by inunction. Further, it was introduced into the cerebrum, nose, throat, stomach, spleen, peritoneal cavity, pleural cavity, and in the

testicle of monkeys. With all these avenues of entrance into the monkey, it was demonstrated that a fair degree of immunity was obtained. No one to my knowledge except Brodie and Kolmer has prepared a vaccine for use in the protection of man. Each of these workers has prepared a vaccine which has proved highly successful in the immunization of the monkey.

Brodie's[2] vaccine contains poliomyelitis monkey passage virus inactivated by the addition of formalin (0.1 per cent) and incubated from twelve to forty-eight hours. Brodie[3] had previously experimented with living virus, virus-serum mixtures, and virus treated by phenol, but his results with these were not as satisfactory as those obtained in the use of formalinized virus. Encouraged by the results which he obtained in the immunization of ten out of twelve monkeys by subcutaneous injections of a 10 per cent suspension of his vaccine, Brodie[4] then inoculated six volunteer laboratory workers, including himself. They were given from one to three doses of (5 c.c.) 10 per cent suspension at intervals of eleven and eight days, respectively. With the exception of a slight induration at the site of the injection in three cases, no untoward effects were noted. A group of twelve children ranging in age from one to six years was then inoculated. Five of the children received one dose of 5 c.c., and seven had two doses. From 1 to 2.5 c.c. of the vaccine was given intradermally, and the balance (4 to 2.5 c.c.) was given subcutaneously. No reactions were observed following the injections except for a slight induration at the site of inoculation. It is interesting to note that in both groups, the six laboratory workers and the twelve children, there was evidence of a small amount of antiviral substance in the blood previous to the injections. Because of the small number of cases in this series, no definite opinion could be formulated. Park[5] in a recent article states that 1,300 children were injected with Brodie's vaccine in the California epidemic and that not one of the children injected developed the disease. It would be interesting to know the number of cases of poliomyelitis and the attack rate for this particular locality. Whether this group of 1,300 children might or might not have developed this disease if not inoculated still remains unanswered.

Kolmer believes with Andrewes[6] that vaccines made of a dead virus are weaker than those of a living or an attenuated virus. He[7, 8] has, therefore, produced an attenuated vaccine of poliomyelitis virus containing a 4 per cent suspension of monkey spinal cord in a 1 per cent sterile sodium ricinoleate solution with which he had successfully vaccinated eighteen monkeys by injecting subcutaneously 0.05 c.c. to 1 c.c. per kilogram and intracutaneously 0.1 c.c., respectively, every five days for ten doses. Later larger doses per kilogram were given, and the number reduced to five. These monkeys have now retained their immunity for three years. This work[9] was followed by the inoculation of himself, his assistant, and a group of twenty-five children ranging in age from eight months to fifteen years, respectively. Three doses were given at weekly intervals. The amount of vaccine given with each dose was 0.25 c.c., 0.5 c.c., and 0.5 c.c. for those under three years of age; 0.5 c.c., 0.5 c.c., 0.5 c.c., and 1 c.c., four to ten years; 0.5 c.c., 1 c.c., and 1 c.c., eleven to fifteen years; and 0.5 c.c., 1 c.c., and 2 c.c., for adults. A small amount of antiviral substances could be demonstrated in ten of the children; fifteen had absolutely no protective substances in their blood serums before the inoculations were given. After the course of treatment the above mentioned ten children showed an increase in their antiviral substances, and the fifteen without protection showed very definite amounts. Therefore, antibody production was demonstrated in twenty-one, or 84 per cent of this group. Several local or general reactions were absent. To date, Kolmer (personal communication) has inoculated about 350 children without any untoward effect.

It is gratifying to learn of the success attained by both Brodie and Kolmer in the use of their vaccine for the prevention of poliomyelitis in the monkey, but time

alone will prove or disprove its value in man. There are several questions which come to mind in this respect.

First, can these vaccines be used with safety during an epidemic? Brodie claims (although some workers are not in accord) that his vaccine is free of any living virus. If this is a fact, it would seem fair to conclude that this vaccine could be used during an epidemic with safety. Kolmer's vaccine, on the other hand, contains attenuated living virus. Since it is known that the attenuated virus is capable of increasing in strength in the human body, would it be safe to introduce this vaccine into a susceptible person during an epidemic? Kolmer believes that it is safe.

Second, is the immunity produced by the injection of these vaccines specific for the human type of virus? It is believed by some that the immunity produced by these inoculations is specific to human virus, but Paul and Trask[10] have recently shown experimentally that this is not always true.

Third, assuming that the immunity produced is specific, how long will it last? In Kolmer's experiments eighteen monkeys have retained their immunity for three years, while Brodie's still showed their immunity when tested three months after inoculation. Is the immunity shown by these animals all due to the use of vaccine? May it not be possible that at least a part of this immunity is due to the natural response of tissues which have grown to maturity?

Fourth, assuming that the immunity is specific and that it lasts at least three years, whom shall we immunize? How shall we distinguish the nonimmune from the immune person? The neutralizing test now in use for this purpose is not practicable because of the time consumed for its completion (two to three weeks) and the financial expense involved. It has been suggested that we immunize the most susceptible age groups.

In Philadelphia there are approximately 133,000 children under five years of age and 170,000 between five and nine years, a total of 303,000 in the most susceptible age groups. The attack rate in 1932 for this group was 198 per 100,000 population. In other words 100,000 children of this age group would have to be immunized in the hope of protecting 198 children or by immunizing every child in Philadelphia under ten years (303,000) we would expect to protect 594 of them. Is this worth while? Does the end justify the means? These questions I leave for you to answer.

It is the opinion of both Kolmer* and Brodie that this problem is not yet solved. I believe that only through the intelligent cooperation of the pediatrist with research workers can the ultimate solution of this problem be reached.

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DR. STANLEY D. GIFFEN (TOLEDO, OHIO).—What is your opinion of this vaccine?

CHAIRMAN TOOMEY.—Brodie bases all his work on what he obtains with his m.c.p., the minimal complete paralyzing dose in the monkey. This point should never

*I wish to express my appreciation to Dr. Kolmer for his kindness in permitting me to have access to his unpublished paper on this topic.

be forgotten. It is the major portion of the syllogism. Those who work with monkey cord virus find it difficult to standardize it without using hundreds of animals to establish an m.c.p. for each new piece of material used. Different cords have different values, even different places from the same cord, and the same cord on different days. When we examine Brodie's papers we find that in some instances his m.c.p. was 0.01, in others it was 0.00125, and in others it was only 0.0003.

It is obvious that there must be an enormous variation in this unit and, if the fundamental variations of m.c.p. in some instances is almost one hundred times, one must get better than a hundred fold protection to denote protection. Does he get this?

In a recent paper, Brodie pointed out the fact that monkeys which had had poliomyelitis got it again when he injected them subsequently. If these animals are not immune after having an actual clinical attack of the disease, how can you expect them to be immunized with small doses of these vaccines?

Kolmer gives a virus which he states is attenuated with sodium ricinoleate, and the monkeys are protected. There is no question but what his monkeys show protection; but I have searched his writings to find out what happened to the negative controls given exactly the same amount per kilogram of unattenuated monkey virus and have failed to find these controls. Perhaps I missed them, but in their absence Kolmer has not proved that the virus is attenuated; if this is so, he has merely repeated what Flexner has shown long ago, i.e., untreated virus vaccine will protect monkeys. Kolmer, however, has gone further, has injected this virus into children, and states that because they show some neutralizing antibodies in the blood serum that this is evidence of protection. The absence of neutralizing antibodies in animals does not mean absence of protection as seen in the rat, cat, horse, mouse, guinea pig. Does the presence of antibodies mean protection? We have seen that monkeys who had the disease were given it again; Dr. Lucchesi states that Kolmer thinks monkeys may not get much protection, but that children will. In short, there is no evidence that a slight increase in antibodies will protect against the disease. If you add to this the fact that no one knows the disease-producing dose in the human being and the fact that there is conflict even as to how the disease is brought about, the only conclusion you can draw is that a number of children have been injected with virus and nothing to date has happened to these children. No one can say it will or will not work.

DR. KRAMER.—The methods for active immunization that have recently been suggested are very much in the experimental stage. In view of past experiences with viruses, there are a number of features in the methods suggested that would cause one to hesitate before the published results have been corroborated.

For example, it is common experience that the best immune response is obtained with active living virus in large doses administered by the intracutaneous route. In the method proposed by Dr. Brodie, not only is the virus rendered innocuous, but the dosage recommended is much smaller than it has been found necessary to employ in the past to obtain adequate immune response.

Virus treated with sodium ricinoleate has not, in our experience, undergone appreciable attenuation. We are dealing with a rare disease; safety is therefore as important a virtue, to say the least, as efficacy.

Since we have no positive proof that the monkey strain of virus employed is fixed, I believe there may be some danger in the use of unmodified virus recommended by Dr. Kolmer.

It is unfortunate that the practicing physician is now placed in the same position with the proposed vaccines as he was a few years ago when human convalescent serum was recommended for therapeutic use. The pressure of publicity compelled

him, often enough, to use convalescent serum, even though he lacked adequate corroborative experimental evidence to justify its use.

The meeting adjourned at four forty-five o'clock.

SUGGESTED OUTLINE FOR APPRAISAL OF FACILITIES FOR HEALTH SUPERVISION AND MEDICAL CARE OF CHILDREN

The following outline has been prepared by the Academy Committee on Child Health Relations as an aid to state groups in reviewing the scope of the problem and in the selection for study or investigation one or more of the phases of the problem which are of first importance in any individual state. The outline covers the following points:

A. The facilities for child health supervision of
   I. Children living in their own homes.
   II. Children in institutions.
   III. Children under care of child-placing agencies.

B. The facilities for medical care of
   I. Children living in their own homes.
   II. Children in institutions.
   III. Children under care of child-placing agencies.

C. Maternal welfare and its relation to child health and welfare.

D. Methods of analysis of data on infant and maternal mortality and morbidity.

E. Special points to be considered in planning and conducting an appraisal.

F. Sources of information.

While an appraisal of the facilities for health supervision and medical care of children should ultimately include all children in a community, district, or state, our first responsibility would appear to be to the children in families unable to procure such supervision and care either for economic reasons or because facilities are lacking, or inadequate, in the community in which they live and to the children who for one reason or another are cared for in institutions or in foster homes. To furnish the information from which plans may be formulated and to insure the provision of more adequate health supervision and medical care for these children is the chief purpose of an appraisal. The appraisal is not an end in itself and, though the Academy Committee on Child Health Relations would be glad to have reports of appraisals or of certain pieces of work that are undertaken so that it can study the methods used and refer them to other state groups desirous of doing something similar, the Committee does not want to convey the idea that it is requesting such an appraisal merely for the collection of data from the various states. It is hoped that an appraisal of this sort will facilitate the discovery of gaps in the state and local child health programs and enable the Academy, either by itself or through state and county medical societies, or both, to cooperate with state and local health departments and officials and with private agencies in improving the health and welfare of children.

In many of the states detailed information can be obtained from the Division of Maternal and Child Health of the State Health Department; in other states that have no active division of this sort, information may be available through the State Health Officer or other officials of the department. In developing plans

for an appraisal, it is suggested that early contact be made with the State Health Department to avoid duplication of work. In some instances, even though certain information is available, it may be desirable to amplify it by further study.

The Committee is offering the outline as one that will be suggestive to the different state groups and one that may be used at first in part and ultimately perhaps in its entirety. It would seem possible for separate subcommittees to work on different phases of the problem at the same time, i.e., on facilities for health supervision of children in their homes, on health supervision and medical care of children in institutions, and on mortality data, etc.

The suggestions are not intended to fit the conditions in any one state, nor will they do so. Sources of information are indicated. Each state group would have to work out its own plan based on its own needs. In no respect are the details complete.

A. Facilities for Child Health Supervision: State and Local

Note: Appraisal of

a. Types of service rendered, i.e., health services to mothers and children and educational program
b. Extent and adequacy throughout state and in local communities
c. Participation by public and private agencies and by individual physicians
d. Evidence of cooperative activities of health, medical and welfare groups

I. Health Supervision of Children Living in Their Own Homes

Public agencies: state-wide

Note: Each agency, whether public or private, state-wide or local, should be studied from the point of view of

a. Organization
b. Personnel and
c. Scope of work: including consultation service; health services; edutional program; special demonstrations; cooperative activities with other state and local departments, professional and lay groups, and private agencies; quality of service rendered; and special groups of children served.

1. State Department of Health, Division of Maternal and Child Hygiene (and other divisions including certain aspects of child health work not covered by division of maternal and child hygiene)
2. State Department of Public Instruction, School Health Services (if under this department)

Note: This is primarily the concern of the Academy Committee on Health of School Children, but it must also be considered as part of a general appraisal of child health activities

3. State Department of Agriculture

Extension Service

4. State Department of Mental Hygiene (or Division of Mental Hygiene in some other department)
5. State Department of Welfare—Bureau of Child Welfare. State Department of Institutions and Agencies

Health supervision of children under care in their own homes, including dependent children (mothers' aid), and children under jurisdiction of juvenile court

Public agencies: local

1. County, city, or district health departments
2. County or city department of education
3. Public clinics

Private agencies: state-wide

1. State-wide agencies employing health workers
2. Professional groups
   Medical societies; public health groups; nursing, nutrition, and home economics organizations; school health physicians, etc.
3. Lay organizations
   Parent-Teacher Associations; Farm Bureaus; Grange; service clubs; American Legion; State Federation of Women's Clubs; Child Welfare League, etc.

Private agencies: local

1. Local private agencies employing health workers: as visiting or public health nursing organizations, crippled children's organization, tuberculosis associations, convalescent homes, maternity homes, day nurseries, orphanages, schools for blind or deaf, etc.
2. Private hospital clinics or dispensaries
3. Local professional groups:
   medical, nursing, public health, etc.
4. Local lay organizations:
   P.T.A., Child Welfare League; service clubs, etc.

Private physicians offering health supervision to children as part of practice

1. Number and qualifications of general practitioners and specialists
2. Distribution throughout state

Adequacy of child health services in state for children living in their own homes

1. Territory served by physicians, public health nurses, extension workers, nutritionists, etc.
2. Character of area having no child health service and possible methods of supplying both medical and nursing service
3. Percentage of child population served under 1 year; 1 to 6 years; 7 to 12 years; 12 to 16 years
4. Completeness of services offered
5. Infant mortality rate; neonatal mortality rate
6. Need of educational program and character of program desired for physicians, nurses and lay groups, including students
7. Adequacy of services to special groups of children
   a. Children in rural areas
   b. Children in families on relief or on borderline of relief
   c. Certain racial groups, negroes, Mexicans, etc.
   d. Children in certain communities, as mining areas, industrial areas, islands off coast, etc.

II. Health Supervision of Children in Institutions

1. Types of institutions
   a. Public institutions: state or local, under Department of Public Welfare, Department of Institutions and Agencies, Department of Public Instruction—caring for
      (a) Dependent and neglected children—state or local county houses, almshouses, etc.
      (b) Delinquent children—farm schools, reformatories, etc.
      (c) Handicapped children—state or local institutions and schools for deaf, blind, crippled, mentally deficient children; sanatoriums and preventoriums
      (d) Children in penal institutions for women and girls

b. Private institutions: state-wide or local—caring for

(a) Dependent, neglected, delinquent children—orphanages, foundling homes, maternity homes, day nurseries, special schools, etc.

(b) Handicapped children—homes and schools for deaf, blind, crippled and mentally deficient children; preventoriums; convalescent homes, etc.

2. Scope of appraisal of health supervision*

a. Medical and dental advisors on board of directors or serving as advisory committee, including specialists

b. Medical staff, general practitioners, specialists; attendings, resident staff.

c. Periodic health examinations, medical and dental

d. Plan for follow-up of recommendations and correction of defects

e. Preventive measures, as immunizations, vaccinations, etc.

f. Dietary adequacy. Supervision by nutritionists? Dietitian? Physician?

g. Daily routine—supervision by physician of hours of sleep? Hours of outdoor play or exercise? Hours of work for children over____ years of age?

III. Health Supervision of Children in Care of Child-Placing Agencies

1. Type of agencies

a. Public agencies—state or local—caring for dependent, neglected, delinquent, or handicapped children: Child Welfare Bureaus of State Departments of Public Welfare, county commissioners or county welfare boards, city boards of welfare

b. Private child-placing agencies—state-wide or local—caring for dependent, neglected and handicapped children

2. Scope of appraisal of health supervision†

a. Medical and dental advisors on board of directors or serving as advisory committee, including specialists

b. Medical Staff, general practitioners, specialists; attendings, resident staff

c. Periodic health examinations, medical and dental

d. Plan for follow-up of recommendations and correction of defects

e. Preventive measures, as immunizations, vaccinations, etc.

f. Dietary adequacy. Supervision by nutritionist? Dietitian? Physician?

g. Daily routine: Supervision by physician of hours of sleep? Hours of outdoor play or exercise? Hours of work for children over____ years of age?

B. Facilities for Medical and Dental Care of Children

I. Medical Care of Children Living in Their Own Homes

1. By physicians in practice

a. Pediatricians, general practitioners specializing in pediatrics, general practitioners with no specialty, other specialists

b. Area of state and percentage of population *not* served by any physician; area *not* served by pediatrician

c. Adequacy of medical care, quality and quantity, especially in rural areas

---

*Suggestive questionnaire for preliminary study of health supervision of institution attached.

†Suggestive questionnaire to be provided if desired.

2. By visiting nurses for bedside nursing care of sick
   a. Number in state, counties, and cities
   b. Area of state, counties, and cities covered
   c. Type of services rendered to children
   d. Adequacy of nursing service for sick children
3. In clinics (usually in cities)
   Public—connected with public hospital or institution
   Private—connected with private hospital or owned and managed by private physicians
4. In hospitals
   a. Types and number of hospitals admitting children
      i. Public or private
      ii. Central or regional
      iii. Special or general
   b. Types of medical or surgical service for children provided by
      i. Centrally located general or special hospitals
      ii. Regional hospitals
   c. Staff: part time, full time, or both; specialists; nurses; social workers, etc.
   d. Adequacy of hospital service to meet needs of state
      i. Distribution of hospitals throughout state
      ii. Number of beds for children
      iii. Staff
      iv. Adequacy of services of different type and of facilities for special procedures
5. In convalescent homes
   a. Number in state and location
   b. Types of service provided, pediatric, orthopedic, etc.
   c. Staff: part time, full time, both; specialists; nurses, etc.
   d. Adequacy of service to meet needs of state
6. Medical and Dental Care of Children in Families on Relief
   a. Number of such children in state, counties, cities or towns needing medical care
   b. By what agencies provided
   c. Given by local private physicians or dentists; by county or city physicians or dentists; in clinics
   d. Adequacy of care

II. Facilities for Medical and Dental Care of Children in Institutions

1. Types of institutions
   a. Public institutions: state or local, under Department of Public Welfare, Department of Institutions and Agencies, Department of Public Instruction—caring for
      (a) Dependent and neglected children—state or local county houses, almshouses, etc.
      (b) Delinquent children—farm schools, reformatories, etc.
      (c) Handicapped children—state or local institutions and schools for deaf, blind, crippled, mentally deficient children; sanatoriums and preventoriums.
      (d) Children in penal institutions for women and girls
   b. Private institutions: state-wide or local—caring for
      (a) Dependent, neglected, delinquent children—orphanages, foundling homes, maternity homes, day nurseries, special schools, etc.

(b) Handicapped children—homes and schools for deaf, blind, crippled and mentally deficient children; preventoriums; convalescent homes, etc.

2. Medical care provided in institution by
   a. Nonresident physicians in practice in community, general practitioners, or specialists
   b. Resident physicians
3. Dental care
4. Nursing care
5. Period of medical observation and care of child on admission to institution
6. Hospitalization of sick children
   a. In infirmary in institution
      Facilities for isolation of communicable diseases
   b. Use of community hospitals. General or special children's hospitals?
7. Use of convalescent home
8. Adequacy of medical care of children in institutions

III. Facilities for Medical and Dental Care of Children Under Care of Child-Placing Agencies

1. Types of agencies
   a. Public agencies: state or local—caring for dependent, neglected, delinquent, or handicapped children;
      Child Welfare Bureaus of State Departments of Public Welfare; county commissioners or county welfare boards; city boards of welfare
   b. Private child-placing agencies: state-wide or local—caring for dependent, neglected and handicapped children
2. Period of medical observation and care before placement in foster home
3. Medical care of children in foster homes
4. Dental care
5. Nursing care
6. Hospitalization
7. Use of convalescent home
8. Adequacy of medical care of children in foster homes

C. Maternal Welfare and Its Relation to Infant and Child Health and Welfare

I. General Maternal Welfare Program in State and Local Community

Public agencies: state-wide

Note: Each agency, whether public or private, should be studied from the point of view of

a. Organization
b. Personnel and
c. Scope of work: including consultation services; health clinic or hospital services; educational program; special demonstrations; cooperative activities with other states and local departments, professional and lay groups and private agencies; quality of care rendered; and special groups of women served

1. State Department of Health, Division of Maternal and Child Health
2. State hospitals and clinics
3. State Relief Administration or State Board of Public Welfare

Public agencies: local

1. County, city or district health departments
2. Public hospitals and clinics
3. County, or city, or other local relief administration or board of welfare

Private agencies: state-wide

1. State-wide agencies employing health workers, as Red Cross or state public health associations
2. Professional groups, as state committees on maternal welfare; medical societies; public health, nursing, nutrition, or home economics organizations and groups
3. Lay organizations, as Farm Bureau, American Legion, etc.

Private agencies: local

1. Local agencies employing health workers; as visiting nurse associations; other public health nurses or maternal welfare organizations
2. Private hospital and clinics, including maternity homes
3. Local professional groups; medical, nursing, public health
4. Local lay organizations

Private physicians offering maternal health supervision as part of practice

1. Number and qualifications of general practitioners and obstetricians; number of obstetricians available for consultation in rural or other areas where there is none
2. Distribution in state

Hospital facilities in state

1. Number of special maternity hospitals, general hospitals with special separate maternity section or wards, hospitals with no special maternity service or wards
2. Distribution in state

Adequacy of maternal health program

1. Territory served by physicians (general practitioners, obstetricians), public health nurses, clinics, and hospitals
2. Character of area not served
3. Percentage of women served by physicians, by midwives
4. Completeness of service offered: prenatal, natal, and postnatal care by physicians and by public health or special maternity nurses
5. Percentage of women hospitalized at delivery and reasons for hospitalization
6. Mortality rates; morbidity
7. Need of educational program and character of program desired, for
   a. Physicians
   b. Nurses
   c. Midwives
   d. Lay groups, including students

II. Maternal Care of Women in Institutions

1. Public penal institutions
2. Private maternity homes

   Adequacy of prenatal, natal, and postnatal care

   (a) Medical care, including availability of consultant service;
   (b) Hospital facilities
   (c) Nursing care
   (d) Social service

D. METHODS OF ANALYSIS OF DATA ON INFANT AND MATERNAL MORTALITY AND MORBIDITY

I. Study of Vital Statistics by State and for Individual Counties, Rural Areas, and Cities, Classes, Trades, etc.

1. Race
2. Age of infant and age of mother
3. Geographic situation of county
4. Residence of mother
5. Cause of death, etc.

II. Collection of Current Data Regarding all Maternal and Infant Births and Deaths (Including Stillbirths) Within Given Time and Area and Study By

1. Economic and social condition, including racial and other special groups in population
2. Medical care and health supervision
3. Age at death and cause of death
4. Facilities for care of newborn infants and especially premature infants
5. Facilities for care of mother—prenatal, natal and postnatal

E. SPECIAL POINTS TO BE CONSIDERED WHEN PLANNING AND CONDUCTING APPRAISAL

1. Plans for cooperation between health, medical and other welfare and lay groups, state and local. Use of advisory committees, state and local.
2. Place of the private physician (including the pediatrician) in the plan
   a. As a leader and active participant in the child health program; and
   b. As a coworker with the health officials; and
   c. As a member or adviser on all committees and boards of directors of any institution or organization caring for children
3. Relation of adequacy of care and maternal mortality to infant and child health mortality. Need for cooperative planning with groups of obstetricians. Studies of current maternal deaths
4. Standards for health supervision of children and mothers in their own homes that may be possible in individual states and local communities
   a. Extent and frequency of physical examinations
   b. Follow-up care by physicians and public health nurses
   c. Immunization programs
   d. Educational program by health, medical, educational, nutrition groups and lay organizations
   e. Other agents
5. Standards for health supervision and medical care of children in institutions and foster homes
   a. Periodic physical examinations, frequency, form
   b. Dietary
   c. Health habits, including mental hygiene
   d. Immunization programs
   e. Provision for care of sick, especially communicable diseases
6. Special problems
   a. Racial, ex., the high infant mortality rate among Negroes, Mexicans, Indians, Chinese, Japanese, etc.
   b. Industrial, ex., textile and other factory workers
   c. Agricultural, ex., tobacco and beet sugar workers

d. Geographic, ex., mountain families, prairie and mining sections, islands off coast, etc.

7. Mortality and morbidity data by counties or districts as indications of health conditions for children and mothers
   a. Importance of neonatal mortality data; data on care of premature infants
   b. "Sore spots" in states, counties, and cities
8. Special problems of health supervision and medical care of children in families on relief
9. Use of ways to show graphically the facilities or provisions for medical care (physicians, hospitals, nurses, etc., or health supervision) and mortality data

F. Sources of Information

I. Public agencies:

1. Federal agencies
   U. S. Census Bureau
   U. S. Children's Bureau
   U. S. Public Health Service
   U. S. Department of Agriculture, Extension Service, Bureau of Home Economics
   U. S. Office of Education
   Federal Emergency Relief Administration
2. State departments
   State Department of Health:
   Division of Maternal and Child Health
   Division of Control of Communicable Diseases
   Division of Sanitary Engineering covering control of water and milk supply
   Bureau of Vital Statistics, etc.
   State Department of Public Instruction:
   School Health Services
   Physical and Health Education
   Department of Vocational Rehabilitation, etc.
   State Department of Agriculture:
   Extension Service—Home Economics Division
   State Department or Division of Mental Hygiene
   State Department of Public Welfare and/or
   Department of Institutions and Agencies:
   Bureau or Division of Child Welfare
   Division of institutions caring for dependent or delinquent children, handicapped children, and children in penal institutions for women and girls
   State Relief Administration
3. Local: county or city
   Departments of health, public instruction, welfare
   County commissioners

II. Private agencies or private with state aid:

1. National organizations concerned with child and maternal health, as
   American Child Health Association
   American Public Health Association
   National Tuberculosis Association

National Organization of Public Health Nurses
American Social Hygiene Association
National Committee for Maternal Welfare
Maternity Center Association, etc.

2. State-wide agencies or organizations: as Red Cross, public health associations, medical societies, organizations of public health nurses, crippled children's societies, special funds; and lay organizations, as P.T.A., Farm Bureau, Grange, service clubs, American Legion, etc.
3. Local agencies: county or city, as visiting or public health nursing associations, hospital clinics, local medical groups and societies, local

III. Questionnaires to individual agencies, physicians, health officers, etc. lay groups, etc.

NEW MEMBERS

The following were elected to membership in the American Academy of Pediatrics at the meeting held in New York, June 7 and 8:

REGION I

Batell, Leo, Forest Hills, N. Y.
Blaugrund, Samuel, Trenton, N. J.
Burns, John B., Binghamton, N. Y.
Bush, Fred W., Rochester, N. Y.
Chappell, Arch. B., Middletown, N. Y.
Cohen, Samuel Adams, New York, N. Y.
Coppolino, John F., Philadelphia, Pa.
Dargeon, Harold W., New York, N. Y.
Frisch, Irving A., New York, N. Y.
Gilmartin, Joseph A., Pittsburgh, Pa.
Hayes, Clara E., New York, N. Y.
Hill, Kyle, Hempstead, N. Y.
Holt, Raymond W., Niagara Falls, N. Y.
Hunt, Frederick C., New York, N. Y.
Hunt, George P., Pittsfield, Mass.
Johnson, John A., Olean, N. Y.
Judelsohn, Louis, Buffalo, N. Y.
Langdon, John, Providence, R. I.
Leonard, George N., Lawrence, N. Y.
Moffett, R. Duryea, New York, N. Y.
Murray, Harrold A., Newark, N. J.
O'Connor, Alfred S., Worcester, Mass.
Park, Edwards A., Baltimore, Md.
Quinn, Thomas R., Pittsburgh, Pa.
Rosenberg, Lester, Brooklyn, N. Y.
Shapiro, Ben, Jamaica, N. Y.
Shaw, Henry L. K., Albany, N. Y.
Taylor, Clifton C., Bridgeport, Conn.
Uhr, J. Stanley, New Brunswick, N. J.
Warren, Robert O. Y., Wilmington, Del.
Weiner, Joseph, New Haven, Conn.
White, George E., Windsor, Ontario, Canada
Wilkes, Edward T., Long Island City, N. Y.
Wolin, David, Rochester, N. Y.

REGION II

Binns, Frazier, Nashville, Tenn.
Chapman, Sims A., New Orleans, La.
Funkhouser, W. L., Atlanta, Ga.
Jarratt, Guy C., Vicksburg, Miss.
Knox, Jos. C., Raleigh, N. C.
Limper, Margaret A., Louisville, Ky.
London, Arthur H., Jr., Durham, N. C.
McMullen, Edwin C., Pine Bluff, Ark.
Melson, Madeline M., Little Rock, Ark.
Meyer, Paul R., Port Arthur, Texas
Phillips, James B., Chattanooga, Tenn.
Sloan, Raymond McKnight, Huntington, W. Va.
Spivey, James L., Fort Worth, Texas
Smith, Lois Weir, Dallas, Texas
Street, Claudius A., Winston-Salem, N. C.
Wilson, Owen H., Nashville, Tenn.
York, Byron P., Houston, Texas

REGION III

Biggs, Alfred D., Chicago, Ill.
Bradley, David J., Cincinnati, Ohio
Carlo, Ernest R., Fort Wayne, Ind.
Chadwick, Ward L., Grand Rapids, Mich.
Foster, L. Fernald, Bay City, Mich.
Gillespie, James B., Urbana, Ill.
Hill, A. Morgan, Grand Rapids, Mich.
Kohn, Samuel E., Milwaukee, Wis.
Roehm, Harold R., Birmingham, Mich.
Russell, James E., Jr., Denver, Colo.
Schermerhorn, Lorenz J., Grand Rapids, Mich.
Shaw, Noel G., Evanston, Ill.
Smith, Lillian R., Lansing, Mich.
Van Schoick, Frank, Jackson, Mich.
Woolery, Homer, Bloomington, Ind.

REGION IV

Clark, Esther B., Palo Alto, Calif.
Dostal, Robert J., Santa Monica, Calif.
Douglass, Frank H., Seattle, Wash.
Hills, Clarence B., Berkeley, Calif.
Jacobus, Lawrence R., Oakland, Calif.
Lathrop, Albert S., Santa Fe, N. M.
Meyers, Edith M., Oakland, Calif.
Netzley, Ralph E., Pasadena, Calif.
Seelye, Walter B., Seattle, Wash.
Stafford, Henry E., Oakland, Calif.
Shaw, William A., Reno, Nev.
Wade, Arthur E., Seattle, Wash.

News and Notes

The joint regional meeting of Regions II and III will be held in St. Louis on November 18 and 19, 1935. Headquarters will be at Hotel Chase, Lindell and Kingshighway Boulevards.

The date of the examination of **The American Board of Pediatrics** at St. Louis will be November 20, the day following the joint regional meeting.

The annual meeting of **The American Board of Pediatrics** was held June 10, 1935, at Atlantic City. Dr. Alfred A. Walker was reappointed by the **American Academy of Pediatrics** to succeed himself as a member of the corporation. All of the directors and officers were reelected.

The following changes in the rules for certification were made, based upon the experience gained from examination and upon the general requirements as adopted by the Advisory Board of Medical Specialties and the Council on Hospitals and Medical Education of the American Medical Association.

GROUP I.—Physicians who have specialized in pediatrics for more than 10 years.

Attention is called to the ruling of the Board that no applicant will be certified in this group without examination after September, 1936. Until this date examination is optional with the Board, and all applicants not strictly confining their work to pediatrics must take the examination. After 1943 Group I will be abolished.

GROUP II.—Physicians who have specialized in pediatrics for from seven (7) to ten (10) years. Applicants must submit evidence of at least one year's hospital training and one year's training in a recognized pediatric center and of continued work in some form of pediatric organization or institution. Examination is required. This group will be abolished in 1938.

GROUP III.—Five years of training after graduation from a class A medical school comprising one of the following:

A. One (1) year's service in a general hospital with two (2) years' service in a pediatric center plus two (2) years' specialized practice.
B. Three (3) years' service in a pediatric center plus two (2) years' specialized practice or training.
C. Two (2) years' service in a pediatric center plus three (3) years' specialized practice in pediatrics including continued work in some pediatric activity.
D. One (1) year's service in a general hospital, one (1) year's service in a pediatric center plus three (3) years' experience in the specialized practice of pediatrics including connection with some pediatric activity.

After *1938* the minimum requirements for Group III will be as follows:

Graduation from a class A medical school.
One year's interne service in a general hospital.
Two years' service in a pediatric center.
An additional term of two years of specialized study and/or practice.

The following men have been certified by the **American Board of Pediatrics** since the last report.

Fred Harold Allen, Holyoke, Mass.
Baird U. Brooks, Durham, N. C.
Charles Edward Conrad, Harrisonburg, Va.
Abe Samuel Finkelstein, Newark, N. J.
Benjamin M. Gasul, Chicago, Ill.
Fairfax Hall, New Rochelle, N. Y.
Paul Harper, New Haven, Conn.

Woodruff L. Crawford, Rockford, Ill.
Brewster Clarke Doust, Syracuse, N. Y.
James Keeley Everhart, Pittsburgh, Pa.
Horace Lester French, Lansing, Mich.
Leo S. Friedman, Cincinnati, Ohio
Thurman B. Givan, Brooklyn, N. Y.
Archie Leland Gleason, Great Falls, Mont.
David Greene, New York, N. Y.
Sidney Valentine Haas, New York, N. Y.
Eliot Hubbard, Jr., Cambridge, Mass.
Lewis A. Koch, Brooklyn, N. Y.
Lambert Krahulik, Brooklyn, N. Y.
Stanley S. Lamm, Brooklyn, N. Y.
Carl H. Laws, Brooklyn, N. Y.
George Nelson Leonard, Lawrence, N. Y.
Thomas J. McElhenney, Austin, Texas
Henry Allen Reisman, Jamaica, N. Y.
Walker L. Rucks, Memphis, Tenn.
Francis Brooking Schley, Columbus, Ga.
Herbert C. Soule, Rochester, N. Y.
Harold Theodore Vogel, Flushing, L. I.
Norman Turner Welford, La Grange, Ill.
Charles A. Weymuller, Brooklyn, N. Y.
George Edward White, Windsor, Canada
Frank J. Williams, Albany, N. Y.
King Grier Woodward, Rockford, Ill.
Arthur Fowler Ackerman, Summit, N. J.
Ward L. Chadwick, Grand Rapids, Mich.
Sidney Shaw Chipman, Norwalk, Conn.
Nathan H. Einhorn, Philadelphia, Pa.
Lee Edward Farr, New York, N. Y.
Marion Gertrude Josephi, New York, N. Y.
Louis Judelsohn, Buffalo, N. Y.
George William Kutscher, Jr., Asheville, N. C.
Martin M. Maliner, Brooklyn, N. Y.
John Walker Maroney, Detroit, Mich.
Laura Elizabeth McClure, Lansdowne, Pa.
Paul Morris, Philadelphia, Pa.
Wilfred S. Nolting, Detroit, Mich.
Merle Pierson, Detroit, Mich.
Alfred Wayland Pinkerton, Dobbs Ferry, N. Y.
Thomas Francis Reilly, Springfield, Mass.
Robert Page Rogers, Greenwich, Conn.
Harold B. Rothbart, Ann Arbor, Mich.
Jacob Lewis Rothstein, New York, N. Y.
Russell B. Scobie, New York, N. Y.
John J. Slavens, Toronto, Canada
Lendon Snedeker, Boston, Mass.
Elwood Wakefield Stitzel, Altoona, Pa.
Haskell Talamo, Worcester, Mass.
Harry Wexler, Brooklyn, N. Y.
Edward Theodore Wilkes, Long Island, N. Y.
Herbert M. Williams, New York, N. Y.
T. Wood Clarke, Utica, N. Y.
Harry R. Litchfield, Brooklyn, N. Y.
Arthur C. Swartz, Albany, N. Y.
Horace Kent Tenney, Jr., Madison, Wis.

In the above group 31 men were certified by examination. At the examination held in Atlantic City, New Jersey, on June 10 and 11, 46 men took the examination and 15 men failed. Of the failures 7 were in Group I, 1 in Group II and 7 in Group III. Of those who passed, 2 were in Group I, 7 in Group II and 22 in Group III.

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